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NOTE

THIS volume comprises the publications of the Bender Hygienic Laboratory based on the work for the year ending August 3, 1906. Some of these have appeared in other medical journals, but for the sake of uniformity all have been reprinted from the Bender Laboratory Number (January, 1907) of the ALBANY MEDICAL ANNALS. The object of again presenting these studies is to bring them in collected form before those especially interested in the laboratory or its work.

RICHARD M. PEARCE,
Director.

THE BENDER HYGIENIC LABORATORY
ALBANY, N. Y., *December*, 1906.

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CONCERNING THE PRODUCTION OF CYTOTOXIC SERA BY THE INJECTION OF NUCLEOPROTEIDS.*

By RICHARD M. PEARCE, M. D.,
Professor of Pathology and Bacteriology,

AND

HOLMES C. JACKSON, Ph. D.,
Adjunct Professor of Physiological Chemistry, Albany Medical College.

(From the Bender Laboratory, Albany, N. Y.)

This investigation was incited by the publication of Beebe's studies[1] which describe the production of specific cytotoxic sera for the liver, kidney and pancreas as the result of treating animals with the respective nucleoproteids of these organs. As one of us[2] had previously made a somewhat extensive study of cytotoxic sera prepared by the injection of various somatic cells, and had reached conclusions which did not justify the views then current concerning the specificity of these bodies, it seemed advisable, in view of Beebe's very definite results, to further pursue these studies.

The Development of Our Knowledge of the Cytotoxins.

It may not be out of place to interpolate here a few words concerning the very definite change in opinion which has occurred during the past few years concerning the specificity of the cytotoxins. Shortly after the early publications of Ehrlich and his associates concerning the production of immune hemolysin, a vast number of publications describing specific sera for practically all cells of the body appeared in rapid succession. In most of these studies an attempt was made to demonstrate a specificity according to morphological rather than receptorial affinity in disregard of the very clear and definite statement of Ehrlich and Morgenroth. Those who denied a morphological specificity based their opinion on the observation that by the injection of cells, as those of the testicle, apparently free from blood, there resulted not only an antiserum for these cells, but also an hemolysin. This was explained by those who believed in morphological specificity by assuming that a number of red blood corpuscles, sufficient to produce a hemolysin, had been injected with the semen. Later, however, the production by a large number of investigators of hemolysin by the injection of fluids entirely free from red corpuscles, as serum and urine, demonstrated the production of antibodies from free

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* Conducted under a grant from the Rockefeller Institute for Medical Research. Read before the Section in Pathology of the British Medical Association, Toronto, August 21 1906. Published also in *Jour. Infect. Dis.*, 1906 iii, 742.

receptors and firmly established Morgenroth's contention that specificity is a matter, not of cells, but of receptors. Despite these very conclusive demonstrations later investigators, who attempted to produce antisera for the cells of various organs, continued to use emulsions of unwashed organs in utter disregard of the presence of free receptors in the organ juices and also without consideration of the antibodies certain to be produced by the red cells normally present. That sera so produced possessed very definite hemolytic and hemagglutinative properties capable of producing lesions (hemoglobinuria, thrombosis, liver necroses) which might erroneously be ascribed to the supposedly specific body was first suggested by Pearce[3] in a study of nephrotoxins and later[2] definitely demonstrated by a study of the action of sera prepared from the liver, kidney, pancreas, and adrenals completely freed from blood by prolonged washing through the blood vessels. Further, the study of sera so prepared and also of sera resulting from the injection of blood serum, bile, and urine, led to the conclusion that "the cells of various organs of the body have, while differing in morphology and function, certain receptor characteristics in common, and that one type of cell may therefore produce antibodies affecting several cells of differing morphology but with like receptor groups." Specificity in the morphological sense could not be demonstrated.

Other investigations with sera prepared from washed organs, especially those of Portis[4] (antithyroid serum) and Woltmann[5] also indicate the non-specificity of the cytotoxins.

Thus, while the study of the cytotoxins has aided and may still aid in the development of our knowledge of immunity and has incidentally offered several valuable methods of experimentally reproducing pathological conditions, it is evident that the sera produced by the injection of mixtures of organ cells have not a degree of specificity sufficient to warrant their further study in the hope of developing therapeutic methods.

Immunization to Nucleoproteids.

In order to prevent the adventitious formation of those bodies resulting from impure methods of immunization and also in the hope of obtaining greater specificity, a few investigators have utilized the proteid constituents of the cell.

Such attempts to produce antisera for somatic cells are limited, so far as we are aware, to those made by Marrassini,[6] Bierry[7] and his associates, and by Beebe. Of these studies the most comprehensive and most recent is that of Beebe.

Marrassini, working with the rabbit and guinea-pig, studied the effect of serum prepared by injecting rabbit's liver nucleoproteid. The changes resulting were, in general, degenerative in nature and similar to those caused by direct injection of the nucleoproteid itself, but usually more severe. The serum affected not only the organ for which it would be assumed it had an affinity, but also, to a greater extent, the kidney. Marrassini concludes that the action of a cytotoxin is of the same nature as that of other poisons of general action, such as potassium chromate, vinylamin, and pyrogallic acid, which are predisposed to affect more especially the excretory organs.

The experiments of Bierry and his associates are few in number and reported but meagerly. In the first communication Bierry describes the action of a serum prepared by injecting rabbits with the nucleoproteids of the dog's kidney. The injection of 20 to 24 c.c. of the serum into the peritoneal cavity of a dog weighing 12 to 15 kilos caused, after three or four days, an albuminuria which reached its maximum on the 10th to the 15th day. The number of experiments is not stated, but mention is made of one dog in which an albuminuria persisted for one and a half months.

Later in association with Pettit, Bierry made a comparison between the action of liver and kidney nucleoproteid sera. Each was found to cause albuminuria and degenerative changes in both liver and kidney, but the kidney serum produced a more severe albuminuria and more marked histological changes in the kidney than did the liver serum. The lesions of the kidney are described as interstitial hemorrhage, congestion of the glomeruli, and granular degeneration of the cells of the tubules with granular tube casts; and those of the liver as congestion and granular and vacuolar degeneration. The authors concluded that the action of such sera is more energetic upon the organ from which the nucleoproteid is derived, but that there is also a definite action on other organs.

In the third investigation Bierry, assisted by Mayer, made a special study of the urine of dogs receiving a liver nucleoproteid serum. They found biliary pigments, lactic acid, and homogentisic acid and demonstrated that, in some instances, the urine had a marked reducing power not due to the presence of dextrose. By various experiments they were able to produce a condition which they considered analogous to alimentary glycosuria and due to the changes produced in the liver by the serum. The histological changes in the liver were those of granular degeneration and fatty transformation. The kidney and pancreas were normal. Albuminuria occurred in two animals, but was slight and transitory. These results appear to contradict those given by Bierry and Pettit in the earlier communication.

Beebe prepared a serum by injecting thymus nucleohiston of the calf which gave precipitin tests for both nucleohiston and nucleoproteid of the thymus. The more important sera were those prepared by treating rabbits with the nucleoproteids of the liver, kidney, and pancreas of the dog. These all gave definite precipitin tests with their respective nucleoproteids and caused agglutination of cell mixtures, but had no lytic action upon the same. They were all markedly hemolytic and hemagglutinative *in vitro* in dilution up to one to five, but did not cause hemoglobinuria when injected into animals.

In testing their cytotoxic action *in vivo* intraperitoneal injections of 2 c.c. per kilo of body weight were usually employed. The kidney serum caused albuminuria and acute degeneration of the kidney without changes in other organs. Albuminuria appeared generally on the fourth or fifth day, increased in amount rapidly and was accompanied by the excretion of abundant hyaline and granular casts.

The liver serum caused granular and fatty changes and focal necroses of the liver with no changes in other organs or in the urine.

The urine of animals receiving pancreas serum caused what Beebe considers a partial reduction of Fehling's solution—"the formation of an abundant green precipitate, but not the typical red deposit of cuprous oxide." Albuminuria did not occur. Histological examination of the liver, kidney, and spleen revealed no changes; a study of the pancreas was impossible on account of imperfect fixation.

The results of these experiments (five with nephrotoxin, three with hepatotoxin and two with pancreas antiserum) provide, Beebe states, "strong indications that cytotoxic sera having a high degree of specificity can be prepared from the nucleoproteids of tissues," and that it is possible "to make a serum which will act primarily on one organ." Further comment on the work of Beebe will be made in the discussion of our own results.

METHODS.

As the amount of detail involved in work of this character is very great, it was considered advisable to limit our investigation to the study of two sera rather than to a superficial study of several. As physiological disturbances are the most satisfactory indications of the injurious action of a serum, antisera were prepared for the kidney and pancreas. The experience of practically all investigators that nephrotoxin is more nearly specific than other sera and the statements of Bierry and Mayer and that of Beebe concerning reducing substances in the urine also influenced this decision.

Rabbits, in groups of three, received in the peritoneal cavity five injections of the nucleoproteids of the dog's kidney and pancreas at intervals of five to seven days; after an interval of ten days the animals were bled. The serum thus produced was injected intravenously into dogs which had been under observation for considerable periods of time and the urine of which had been carefully examined daily.

As a control of the supposedly specific nucleoproteid sera, in order to determine if nucleoproteid serum may not have a general toxic action on animals other than that from which the nucleoproteid was prepared, rabbits were injected with the nucleoproteid* of the pancreas of the cow and the effect of this serum was tried on the dog.

As a further control, and in order to determine also whether or not antisera for nucleic acids could be obtained, rabbits were injected with the nucleic acids of the dog's pancreas and kidney.

The preparation of the nucleoproteids.—In the preparation of the nucleoproteids we have employed one of the methods recommended by Levene. This seemed particularly advantageous for two reasons. In the first place the heating of the glands to the boiling-point effectually eliminates all possibility of future autolysis, while on the other hand, the increased ease with which the solutions filter decreases the time of preparation. We are fully aware that the various nucleoproteids respond with different degrees of ease to extraction, but the point we had in view was not to obtain the maximum yield of material, but to endeavor to produce in the shortest time the purest product possible.

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* For this material we wish to thank Professor J. A. Mandel, of the University and Bellevue Hospital Medical School.

Emphasis must be laid upon the fact that only blood-free organs were employed. In this direction extreme care was exercised since the exclusion of all proteids of blood origin must be of prime importance where specific gland products stand in question. By inserting a cannula into the aorta below the renal arteries and laying a ligature above the coeliac axis, an irrigation of $\frac{n}{7}$ NaCl solution was established by means of which the blood was thoroughly removed from the organs. The blood-free organs immediately removed from the animal and cut into fine pieces were pressed with a mortar and pestle through a fine-mesh sieve and the finely comminuted material mixed with from two to four times its weight of water. The gland in suspension was then brought to the boiling-point in an Erlenmeyer flask of appropriate size. After allowing the mixture to cool it was quickly filtered through a double-folded filter. The first few cubic centimeters of filtrate, invariably turbid, were thrown on the filter again until a clear fluid resulted. The product of from one to two hours' filtration might be said roughly to correspond to the amount employed in each preparation. To this was then added acetic acid until complete precipitation resulted, the amount necessary varying according to the kind of nucleoproteid. Under ordinary circumstances the nucleoproteid separated out as a fine white flocculent precipitate; only once did it become necessary to add alcohol to bring about the precipitation of this character. This precipitate was washed with distilled water by sedimentation until the washings did not respond to the biuret reaction. This procedure in the absence of a centrifuge such as that described by Beebe was accomplished in four to five hours. In order to hasten the process, siphonage of the supernatant fluid took place before complete sedimentation had been accomplished even at the risk of loss of material. The material was then suspended in water and put into solution with the smallest possible amount of sodium carbonate; the resultant solution when filtered gave a clear filtrate which was reprecipitated with acetic acid, washed several times by decantation, and dehydrated with alcohol and ether. The products were white powders. That derived from the pancreas contained 1.74 per cent P; from the kidney 2.10 per cent P.

Just previous to each injection the required amount of the powder was weighed out and dissolved in an appropriate amount of sterilized 0.5 per cent sodium carbonate into which solvent it passed readily.

It seemed to us distinctly disadvantageous that the substance should be kept in solution for any length of time even by employing cold or antiseptics as precautions against autolysis or bacterial action. That changes of a certain character do take place under such circumstances is evidenced by the fact that Beebe noticed that a fine deposit settled out in his solutions after some weeks. In only one instance in our investigation was the injection made later than a few hours after preparation of the solution. It would be hard to give absolute figures of the actual time consumed in the preparation of the various products. Excluding the period of cooling over night, when the gland stood in a condition free from the possibility of autolysis, the procedure occupied 15 hours, most of which time, however, the material was suspended in water. This period, especially in view of the fact of the initial stoppage of autolysis, would not allow sufficient time for change of the character so guarded against by Beebe. In our opinion this precaution is undoubtedly necessary, but not of the extreme importance assumed by him. The freedom of the products from blood or protoplasmic proteid impurities would seem to be the goal for which to aim.

If, with Kossel, we assume that the present nucleoproteids or nucleins are in part laboratory products not originally present in the cell but formed in the process of the separation, the proteid moiety of the compound must be derived from protoplasmic substance as distinct from the chromatin, but not necessarily different from the cell proteids (globulins or albumins). If such is the case the question as to the specificity of nucleoproteids as such must be ruled out and the proper direction to train investigation would be to attempt to prepare antibodies from various cell-proteids or nucleic acids prepared as pure as possible. The former point we still have in mind. As Beebe states, from the analysis of his preparations it is evident that the products employed by him are not true nucleoproteids but nucleins, and the molecule of the so-called protein nucleate possesses relatively less of the proteid and more of the nucleic acid radical. He also mentions that the color proteid reactions were given in only a feeble way. Certainly it would seem that the results obtained by the use of such products should be ascribed more probably to the nucleic acid than to the proteid radicals.

The products prepared by us contained less phosphorus than his, pointing to a higher proteid content, and gave characteristic results when tested with Millons, biuret, Adamkiewicz, and Molisch reactions. These reactions could not be ascribable to cell-globulins, which were removed in the process of preparation.

It seems rather dangerous to draw conclusions as to the intravenous clotting obtained when products prepared from organs containing blood are injected in the blood stream. The possibility is always at hand of the presence of fibrin ferment, thrombin, nucleohiston, or whatever may be the agent active in setting about the changes which result in the formation of fibrin in the blood. It is, we think, at present questionable whether it has yet been definitely shown that nucleoproteid, absolutely free from contamination of blood in the general sense, will cause intravenous clotting.

The preparation of the nucleic acids.—The method employed for the preparation of the nucleic acids from the pancreas and the kidney of the dog was essentially that of Levene. The finely comminuted gland was boiled for two hours in a 5 per cent solution of sodium chloride after which sodium acetate in the proportion of 7 per cent of the weight of the fresh glands was added and the mixture allowed to cool. Sodium hydroxide was next added in excess and the material allowed to stand over night. After the reduction of the greater part of the alkalinity with acetic acid the faintly alkaline mixture was precipitated with an excess of picric acid and acetic acid carefully added until a well-formed flocculent precipitate settled out. This filtered quickly. The amount of acetic acid necessary at this point varies according to the kind of nucleic acid. The proteid-free filtrate was next thrown in a large volume of 95 per cent alcohol, and allowed to stand until the nucleic acid settled out. The major part of the alcohol could be removed by siphonage and the precipitate collected on paper. The precipitate was again dissolved in alkali in the presence of sodium acetate and acidulated with acetic acid. A slight precipitate was filtered off. To the filtrate saturated with sodium chloride was added hydrochloric acid until the mixture reacted acid to congo red when an equal volume of alcohol was added. This precipitate showed itself to be biuret free and was dehydrated with alcohol and ether. The products contained from 8 to 9 per cent phosphorus. As was the case with the nucleoproteids, the necessary amount of the substance was dissolved in an appropriate amount of 0.5 per cent sodium carbonate and injected within a few hours after preparation.

Detail of Experiments and Results.

In all instances the dogs received in a small branch of the femoral vein a uniform dose of 2 c.c. of serum per kilo of body weight. The injections were made under light ether anesthesia and the experiment terminated by bleeding from the femoral artery under light chloroform anesthesia. In each group animals were killed at intervals of four, eight and ten days. Five animals received dog's kidney nucleoproteid serum;* five, dog's pancreas nucleoproteid serum; four, cow's pancreas nucleoproteid serum; three, dog's kidney nucleic acid serum; and three, dog's pancreas nucleic acid serum.

Histology.—In no instance did postmortem examination reveal definite macroscopic lesions. The histological study was limited to the kidney, pancreas, and liver. Tissues were fixed in formalin and in Zenker's fluid; the former were examined for fat by the frozen section and Scharlach R method, the latter were embedded in celloidin and stained by hematoxylin and eosin. Fatty changes were not constant, and, when present, of but slight degree. In the kidney nucleoproteid series, fatty changes were found in the kidney series once (10th day) and in no other organ. In the dog's pancreas nucleoproteid series very slight fatty changes were found in three—in one, in liver, kidney and pancreas; in one, in liver and kidney; in the third, in kidney only. The cow's pancreas series gave negative results by this method. On the other hand, in the nucleic acid series fatty changes in the kidney were constant and well marked, affecting uniformly the loops of Henle. All the other organs were negative except for slight changes in the liver in one animal of the kidney nucleic acid series.

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* In preparing the various sera, the average amount of dog's kidney nucleoproteid to each injection was 0.11 gram; of the dog's pancreas nucleoproteid, 0.13 gram; of the cow's pancreas nucleoproteid, 0.15 gram; of the dog's kidney nucleic acid, 0.25 gram; and of the dog's pancreas nucleic acid, 0.11 gram.

In the study of the Zenker hardened material, in no instance were changes in the pancreas found. The liver, although devoid of well-marked lesions, such as necrosis, almost constantly exhibited a peculiar change affecting all parts of the organ. This condition, which has been noted frequently by one of us as the result of the injection of various cytotoxins, and which unquestionably is that described by other investigators as a granular, vacuolar, or fatty degeneration is characterized by a swollen, pale, "washed-out" appearance of the liver cells with a few large, coarse granules and large irregular pale areas which stain but faintly or not at all. The latter areas are not of the character of fat vacuoles, but more irregular, vary considerably in size, and have no definite relation to the nucleus. The appearance is similar to that of liver cells containing glycogen, and as the same condition in marked degree was found in the adrenal, we are inclined to consider it as an abnormal accumulation of glycogen. Unfortunately this explanation did not occur to us until near the close of our experiments and proper routine tests were not made. Upon the basis of a single attempt to isolate the glycogen from the last dog of the kidney nucleic acid series, it can be stated, however, that a greatly increased amount of glycogen was present. This was determined by extracting the finely divided gland with hot water and filtering. The filtrate appeared milky white, gave the iodine reaction for the glycogen, which could be precipitated with alcohol at 65 per cent. No particular haste was employed in getting the organ into boiling water and the fact that the glycogen remained so long postmortem points either to a large excess of the compound or perhaps to the absence or great diminution during life of the enzyme in the liver which transforms the glycogen.

The changes in the kidney were purely degenerative in character, of slight degree, and almost constantly present. The cells of the tubules, especially of the convoluted tubules, were swollen and very granular with more or less definite reticulum. As a rule the nucleus could be readily seen, but in the more marked conditions it stained poorly. Rarely the entire lining of a tubule could be seen separated from its basement membrane and lying free in the lumen as a poorly straining granular ring. In addition to these changes the tubules of the cortex, and less frequently, the straight tubules contained the finely granular reticulum so commonly associated with the milder disturbances of the kidney. In the straight tubules this material was often so compressed as to suggest finely granular casts, but definite casts were found but twice and only in the kidney nucleoproteid series. In the collecting tubules and especially in the loops of Henle, in some instances, a more or less marked vacuolization was present corresponding to the fatty change determined by the use of Scharlach R. In no kidney were glomerular changes found.

It is difficult to distinguish sharply between the types of kidney lesions caused by the different sera. In general the changes due to nucleoproteid sera were more severe and widespread than those due to the nucleic acid sera. The latter were characterized by a greater degree of fatty change and by a tendency to involve the loops of Henle rather than the convoluted tubules. If the presence of casts be taken as a criterion the lesions due to the dog's kidney nucleoproteid must be judged the most severe. It is a matter of considerable importance that the cow pancreas serum, in no sense specific, caused lesions in the kidney not to be distinguished from those due to other sera.

Examination of the urine.—The animals, fed on dog biscuit, were kept in cages suitable for the collection of their urine. This was examined daily for proteids and reducing carbohydrates. The clear filtrated urine was heated to boiling and the merest trace of acetic acid added. This indicated in a roughly quantitative way the amount of coagulable proteids (albumin and globulin) present. It is almost a constant occurrence to find traces of such appearing at variable and irregular times in dog's urine. By traces we mean that upon the addition of acetic acid a faint turbidity appears, which is in no sense a precipitate, but which in the course of 24 hours settles out at the bottom of the tube as a small light fluffy cloud. A second portion was tested with potassium ferrocyanide and acetic acid. The clear urine acidulated with the acid was treated with one drop of the dilute reagent. It was the unusual occurrence to find this test absolutely negative in the dogs under examination in this series of experiments and this result has been confirmed in the examination of many of the urines of other animals at different times. The urine of dogs, concentrated as it is in the passage of an excessively long system of tubules, carries down with it from the collecting tubules not inconsiderable quantities of proteids of the mucin and nucleoalbumin type, which show themselves by the latter test. At times the result of this reaction amounted to a definite flocculent precipitate. With the possible exception of the urines of two of our dogs injected with kidney nucleoproteid anti-serum we feel assured that at no time did our tests give evidence of an excretion of proteid which could in any sense quantitatively or qualitatively be ascribed to changes in the kidney.

In the case of Dog 14 injected on May 20 the urine collected on the 24th showed with heat and with potassium ferrocyanide a decided flocculent precipitate which would be called a positive reaction. The same is true for Dog 15 injected on the same day, the urine reacting positively to both tests on the 25th. Other than these, no results were obtained which would compare in any way to that described by Beebe, where 53 per cent of the urinary nitrogen appeared in the form of albumin. The quantity of proteid in the cases cited was so small that no attempt was made to determine whether it was an albumin or globulin. At no time were casts obtained in the urine, but upon histological examination of the kidney of Dog 15 as in one other dog (17) of this series, a few hyaline casts were seen in the tubules.

In a paper read this year before the American Medical Association by Robertson and Hacker, and based upon work done in this Laboratory, attention was called to the frequent appearance in human urines tested by Fehling test solutions, of a yellowish-green coloration which varies in intensity from the merest opalescence to a definite, finely divided precipitate which in the course of some hours settles out slowly to the bottom of the tube. It was then stated that this reaction is the result of the addition of too much urine in performing the test and must undoubtedly be ascribed to the presence in the urine at times of some weakly reducing compounds capable in large quantities of partially reducing copper solutions. This pseudo-reaction never occurs when there is employed a small amount of urine, sufficient, however, to show dextrose if present. In testing the urine of dogs these remarks are extremely to the point. When 10 or more drops of the filtered dog's urine were added to the two or three times diluted and boiling Fehling's solution and the mixture boiled a few seconds, it was not at all uncommon to notice in a few moments the appearance of a greenish-yellowish haze which gradually became more opalescent and opaque and which, in extreme cases, might resolve itself into a greenish or yellowish precipitate settling to the bottom of the tube, sometimes immediately, or, more frequently, if left standing, over night. This reduction is not due to dextrose; the urine showed no difference before or after fermentation, polariscopically; no osazone could be obtained, and Nylander's test resulted negatively. If on the other hand, only two or three drops of the urine were added to the diluted Fehling's solution in the ordinary way and not boiled after the addition of the urine the test remained negative. All of the urines tested for dextrose in the latter way, during the course of our experiments, showed absolutely negative results, while the pseudo-reaction was obtained more or less irregularly in 16 of the 20 dogs studied. In our opinion this pseudo-reaction has no direct bearing on the subject under discussion. In the case of one dog a continued pseudo-reaction was obtained which could be explained by the elimination of lactose following the removal of puppies during lactation. The negative results of Fehling's test with the urine of this animal indicated beautifully the fact contended for in the paper alluded to above, that Fehling's test performed as there advised can be employed without hesitation as a criterion for the presence of dextrose as against other reducing bodies. In none of the urines examined in these experiments was dextrose present in amounts which could be said to exceed the normal, granting that traces of reducing compounds, perhaps dextrose, do appear ordinarily.

While we cannot of course state positively, still it must be granted that it seems extremely likely that the reduction which Beebe describes as a "partial reduction of Fehling's solution" with "the formation of an abundant green precipitate" was nothing more or less than the pseudo-reduction which we have so frequently observed in the urines of normal dogs. As the manner in which his tests were performed or semi-quantitative details are not outlined, such explanations must be classed as only suggestive but not positive. It is our experience that the urines of the dogs injected with dog's pancreas nucleoproteid antiserum show no different character, as regards the content of reducing carbohydrates, than those treated with any of the other sera.

CONCLUSIONS.

In so far as conclusions from so small a number of experiments are justifiable, our results do not support the theory that specific cytotoxic sera may be developed by the injection of nucleoproteids but indicate, rather, that such sera have certain mildly toxic properties acting in a general way and affecting especially the principal excretory organ, the kidney. In this regard we are in accord with Marrassini and in a general way with Bierry and his associates, but in direct conflict with Beebe's very definite statements.

It is clearly evident, however, that Beebe's claims for a specific pancreas serum based on the demonstration of reducing substances in the urine, especially in the absence of histological changes in the pancreas, is untenable in view of our experience with like reducing substances more or less constantly present in the urine of normal dogs.

We can make no definite statement concerning nucleoproteid hepatotoxic serum, as we did not prepare such, but it is difficult to explain the focal necrotic lesions of the liver, caused by Beebe's hepatotoxin, as a result of the action of a substance which should, presumably, affect the liver cells more diffusely. It may or may not be a matter of importance that his nucleoproteids were prepared from organs but roughly washed in running water and, therefore, especially as regards the liver, containing large amounts of blood. That a very toxic nucleoproteid may be obtained from red blood cells is well known and it is possible that, as a result, Beebe's serum may have contained hemolysin and agglutinin due to this substance, in addition to the supposed hepatotoxin, in sufficient amount to cause focal liver necroses through agglutinative thrombi, as has previously been described by one of us.[8]

Beebe states that all his sera "are markedly hemagglutinative and hemolytic *in vitro* in dilution up to one to five, but in dilution of one to twenty or above no difference is to be detected between the immume and the normal serum." The hemolytic and hemagglutinative powers of our nucleoproteid sera (the nucleic acid sera were not tested) were much weaker. Thus the dog's pancreas nucleoproteid serum, for example, had very slight power to hemolyze or agglutinate red cells. Two parts of the pure serum to one of dog's blood caused neither hemolysis nor agglutination, while 10 parts were required to cause but a faint hemolysis; with the same amount a very definite fine agglutination was evident only after five minutes. It would appear, therefore, by comparison, that the use of blood-free organs in the preparation of nucleoproteid sera lead to the production of a serum less hemotoxic than those developed by the use of unwashed organs. Under such circumstances, therefore, it is very important that future investigators of nucleoproteid sera work with blood-free tissues.

The changes in the kidney resulting from the administration of the kidney nucleoproteid serum, while very definite, cannot be considered as specific or even "special," for similar changes, often of the same grade, characterized the action of all other sera, even that prepared from cow's pancreas. These changes are, therefore, to be regarded as the effect of the excretion of toxic substances rather than as the manifestation of a selective action of the serum. It must be admitted, however, that it is difficult so to explain the severe albuminuria described by Beebe.

Finally, attention must once more be called to the importance, in all investigations of cytotoxic sera, of the use of blood-free organs, to the occasional occurrence of copper-reducing compounds in the urine of apparently normal dogs, to the not infrequent spontaneous nephritis in these animals, and to the possibility of albuminuria due to a catheter cystitis.

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THE CHEMISTRY OF ATHEROMA AND CALCIFICATION (AORTA).*

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This investigation owes its inception to an attempt to study by micro-chemical methods the sequence of the changes occurring in the experimental lesions produced in the rabbit's aorta by the administration of adrenalin. As however micro-chemical methods proved unsatisfactory and analytical methods impossible, on account of the small amount of substance in the rabbit's aorta, the work, as originally planned, was abandoned in favor of a study by analytical methods of the chemistry of the various stages of arteriosclerosis in the aorta of man. The studies of Klotz,[1] which appeared shortly after the beginning of the work, and those of Wells,[2] which were published previous to its conclusion, are so recent that they render a general survey of the literature of calcification unnecessary.

As this work has to do mainly with the relation of the fatty acids and lecithin[3] (phosphorus) to calcification, the results of Klotz and Wells have a very important relation and the views of these investigators may be briefly stated at this time. Klotz employing chiefly micro-chemical methods, believes he has demonstrated that the fatty acids play an important part in calcification. In a few qualitative examinations of calcified material he found what appeared to be calcium soaps. These observations he attempts to support by micro-chemical studies which, however, are not convincing. His demonstration of soaps depends on a peculiar staining with Sudan III, of calcium—principally upon a black discoloration with an aqueous solution of silver nitrate (Kossa's stain). The occurrence in close contact of granules staining by each of these methods is taken as evidence

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* Conducted under a grant from the Rockefeller Institute for Medical Research. Published also in *Jour. Med. Research*, 1906, xv.

[1] KLOTZ, O., Studies upon Calcareous Degeneration, I. The Process of Pathological Calcification, *Jour. Exper. Med.*, 1905, VII, 633.

[2] WELLS, H. G., Pathological Calcification, *Jour. Med. Research*, 1906, xiv, 491.

[3] The term is meant to include all kinds of lecithins or lecithans.

of the presence of calcium soaps and the conclusion is drawn that the formation of these soaps is the first step in the process of calcification. The inaccuracy of this method of investigation has been pointed out by Wells, who, using purely analytical methods, reaches a different conclusion. He finds there is no essential difference between the processes of normal ossification and pathological calcification. No evidence was obtained to indicate that calcium soaps form a constant and important stage in the process of calcification. That they may be present in small amounts is not denied. His experimental studies also speak strongly against phosphoric acid, arising from decomposed nucleoproteids, as an important binder of calcium.

Material.—The investigations here to be described deal with the study of nine aortas. Of these three were normal, two were aortas with extensive atheroma but no macroscopic evidence of calcification, and four showed various grades of calcification. One of these latter was the seat also of large "atheromatous ulcers." As several of the points studied have been covered by Wells' recent publication, these results will be stated but briefly.

Methods.—The preparation of the material was as follows: The entire aorta from heart to division of the iliacs was removed and the intima and media carefully separated from the adventitia in order to exclude all extraneous fat. The material was now cut into small pieces, dried in absolute alcohol over a water bath, ground to a powder, and then placed in a flask with reflex condenser and boiled with absolute alcohol for periods varying from twenty-two to fifty-four hours and afterwards extracted in the Soxhlet apparatus for from nine to thirty-one hours. To facilitate extraction, the material was reground every twelve to fifteen hours and fresh alcohol added. The powdered residue was now extracted in boiling chloroform from twenty-two to thirty-four hours and in the Soxhlet apparatus seven to fourteen hours. The use of ethyl ether, which was one of the solvents first employed had to be discontinued on account of the fact that numerous specimens reacted acid to phenolphthalein. Since this indicator served in the determination of the fatty acids, a neutral solvent became extremely essential. The extractive material taken up in absolute alcohol, boiling absolute alcohol and chloroform was in each case entirely soluble in these solvents. An analysis of the extract was then made for calcium soaps, fatty acids and lecithin as follows: To be absolutely certain of the solubility of calcium soaps, calcium stearate was prepared artificially. It was found to be sparingly soluble in cold absolute ethyl alcohol, considerably soluble in hot absolute ethyl alcohol, but insoluble in chloroform. According to Wells, "calcium oleate is less soluble in ether than in alcohol and the palmitate and stearate dissolve very little in ether, although considerably in ethyl alcohol; all dissolve much better in amyl alcohol, probably largely because of its high boiling point." According to the method of extraction, the calcium soaps should become soluble in the absolute alcohol and appear in the extractive material. The extracts were tested for Ca by fusing with sodium hydrate and potassium nitrate, precipitating with ammonium oxalate and weighing as CaO. The fatty acids were titrated in alcoholic solution with alcoholic $\frac{N}{10}$ NaOH using phenolphthalein as indicator.

Since the phosphorus contained in the alcohol-chloroform extracts was wholly organic in character, it could be considered that the P-content depended upon the presence of some form of lecithin.[1] The P_2O_5 content of the extracts was therefore determined by fusion, precipitation with molybdate solution, magnesium mixture and weighing as pyrophosphate and then calculated as distearyl lecithin. The remainder of the extractive material was estimated as neutral fats. The residue, remaining after extraction, was examined for Ca, Mg and P_2O_5 by the ordinary analytical methods. In making comparisons with other work, however, we must emphasize the fact that the residue of the entire aorta was used and not merely isolated calcified areas.

I wish here to express my indebtedness to Dr. Holmes C. Jackson, Director of the Laboratories of Physiological Chemistry and Experimental Physiology of the Albany Medical College, without whose instruction and supervision this investigation would have been impossible.

Results—I. Calcium soaps. As far as we were able to determine, no calcium soaps, or only mere traces, were to be found in normal or pathological aortas. This was definitely shown in the following manner. Extracts of the aortas which were completely soluble in absolute alcohol gave no reaction for calcium. Extracts, with supposed calcium content, dissolved in chloroform without leaving a trace of residue. As mentioned before the soap, calcium stearate, is insoluble in chloroform.

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[1] DUNHAM, E. K., *Proceedings of the Soc. for Exp. Biol. and Med.*, 1904, I, 39.

II. Fatty acids and Lecithin. These will be considered together.

NORMAL AORTAS.

	Dried Substance—Per Cent.		Fatty Extractive—Per Cent.		
	CaO.	Fatty Extractive.	Fatty Acid.	Lecithin.	Neutral Fat.
1	1.4	20.3	6.1	18.3	75.6
2	.3	11.9	5.73	16.3	77.97
3	....	....	6.18	15.9	77.92

The surprisingly large percentage of lecithin is directly in line with the results obtained by Dunham* in his study of the normal kidney. He found that twenty-seven to thirty-seven per cent of the fatty extract was present in the form of lecithin.

Considering now the degree of calcification in the diseased aorta (the difference in calcification can be determined definitely by difference in calcium content of the residue) a striking relationship of the fatty acids, and especially of lecithin, to the grade of calcification is noticed. This is shown in the following table in which the analyses are arranged according to the calcium content; the last two being those in which no calcification was evident macroscopically.

DISEASED AORTAS.

	Dried Substance—Per Cent.		Fatty Extractive—Per Cent.		
	CaO.	Fatty Extractive.	Fatty Acid.	Lecithin.	Neutral Fat.
1	11.9	22.5	9.6	16.6	73.8
2	7.5	30.	13.9	19.06	67.04
3	7.2	22.4	19.9	24.2	56.7
4	3.8	28.3	21.9	20.9	57.2
5	1.7	8.1	20.2	37.9	41.9
6	1.4	9.4	25.1	52.2	22.7

It is seen that the fatty acids and lecithin are present in greatest amount in the atheromatous aortas without gross evidence of calcification and that as the calcium content increases they rapidly diminish in amount. The remarkable increase in the amount of lecithin and fatty acids which appears at the initial stage of calcification certainly lends evidence to the fact of a decided "fatty" transformation occurring at this time. The fatty acids and lecithins here may or may not have a common origin. The parallelism in their appearance points to the probability that they do. The fact that lecithin and fatty acids may arise from a decomposition of substances of the "protagon" type which Dunham has shown to exist in surprisingly large amounts in the normal cell further substantiates this idea. The second stage in the fatty transformation consists in the disappearance of the lecithin and fatty acids coincident with the increasing calcium content of the tissue. The fatty acids probably react with the alkalies furnished by the blood and pass out of the cell as soluble compounds. The lecithin undergoes decomposition, liberating its phosphate radical which serves either in part or entirely as the conjugant of the calcium.

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* Loc. cit p. 40.

III—*Neutral Fats.* The remainder of the fatty extractive was calculated as neutral fats. The results are shown in the above table. This procedure is not absolutely correct, since necessarily numerous lipoids were present; for example, beautiful tests for cholesterin were obtained.

IV—*The Residue.* Unfortunately, it was impossible to examine only calcified areas for calcium, phosphates and magnesium and at the same time to use all the material for fat analysis. Instead, the residue of the entire aorta was used. The entire P_2O_5 estimated was considered as combining with MgO and CaO to form $Mg_3\ (PO_4)_2$ and $Ca_3\ (PO_4)_2$. The remaining CaO was estimated as $CaCO_3$. In the aortas of lower calcium content, there was relatively a small quantity of $Ca_3\ (PO_4)_2$ while as calcification proceeded, the proportion of calcium phosphate to carbonate increased. For instance, in an aorta with estimated 3.8 per cent Ca content, the relationship between the $Ca_3\ (PO_4)_2$ and $CaCO_3$, was as 69.5 to 25; that with 7.5 per cent Ca content as 74.7 to 24.8; and that with 11.9 per cent Ca content, as 79.9 to 19.9.

As the calcification proceeded, however, the magnesium content decreased, being present in the more calcified areas as 0.1 per cent and 0.32 per cent.

Comparisons. Comparing our results with those of Klotz and of Wells:

1. They differ from those of Klotz, in that by analytical methods we were unable to find the calcium soaps which he claims to have demonstrated by micro-chemical examination but are in accord with Wells' results in this regard.

2. The inorganic analysis of the residue differs, however, from that of Wells. Possibly this is due to the fact that the entire aorta was used. Such material necessarily included both calci-

fied and normal areas, thus diminishing the absolute percentage of calcification. Again Wells examined a different kind of tissue (lymph node) and it is not impossible that the somewhat higher P_2O_5 content obtained by him is due to the presence of the phosphorus containing proteids or their decomposition products which are known to be present in such tissue in relatively large amounts. The $Ca_3(PO_4)_2$ percentage was lower and the percentage of $Mg_3(PO_4)_2$ much less. The figures do not show the very close relationship to normal ossification which is so evident in his results.

CONCLUSIONS.

1. The absence of calcium soaps in the extracts of all aortas examined leads us to the conclusion that in pathological calcification, of the aorta at least, the formation of calcium soap is not an intermediate process.

2. The analyses of the residues apparently point to the fact, insisted upon by Wells, that in pathological calcification, the inorganic salts are deposited in approximately the same proportion as in normal ossification. This does not necessarily signify, however, that the initial processes, from which pathological calcification and normal ossification result, are identical.

3. The remarkably high percentage of lecithin in the initial stage of calcification and the fact that with increasing calcium content there occurs a coincident diminution in the percentage of lecithin has led us to suspect that the phosphate radical may be supplied from a decomposition of lecithin.

ACTION OF CERTAIN DRUGS ON THE ELIMINATION OF URIC ACID DURING A NITROGEN-FREE DIET.*

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The extreme divergence of opinion which exists, based chiefly on a contradiction of experimental results, in regard to the metabolic disturbances commonly associated with the deposition of urates in specific localities of the body has frequently been the stimulus for further work along lines tending to the possible elucidation of this problem. It seemed probable to us that a fruitful line of inquiry lay in the attempt to determine what changes would appear in the nitrogenous composition of the urine of persons nourished with nitrogen-free food during the period of administration of such drugs (colchicum, sodium salicylate) as are most valued in the general treatment of gout or more especially of its seizures.

The fact that alcohol in its various forms apparently is a factor in causing disturbances in the normal elimination of the nitrogenous constituents of the urine and its well-known relation to the appearance of gouty tendencies influenced us to re-examine its effects with the view of comparison and possible confirmation of the work already carried out in this direction. In regard to the literature which has developed on these subjects within the past ten years it may be stated that many, if not all, of the experiments conducted before the time of our knowledge concerning the importance of the distinction between " endogenous " and " exogenous " eliminations, involving, as this does, the important question of diet, must be ruled out as useless. Experimentation is constantly hemmed in by faulty or inexact methods. Unfortunately each advance in the direction toward accuracy

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* Work conducted under a grant made to the Bender Laboratory by the Committee on Scientific Research of the American Medical Association. Published also in *Jour. Amer. Med. Assoc.*, 1906, xlvii.

sets the seal of questionable usefulness on older pieces of experimentation.

In the discussion we will here confine ourselves to the possible explanations of the results which have been obtained by others and those which we reached as the effect of the giving of alcohol, colchicum and sodium salicylate at a time when the nitrogenous elimination was, so to speak, of almost maximum endogenous origin, i. e., during the period of non-nitrogen diet.[1]

Our experiments were carried out on the writers and Dr. J. F. Robinson, assistant in surgical pathology in the Bender Laboratory, who kindly volunteered to aid us and to whom we wish to express our grateful indebtedness.

DIETS.

During the preliminary purin-free period, the diet consisted of eggs, milk, potatoes and bread, the quantities being only approximated in the case of the three subjects and during the three days of the period. The results, however, were sufficiently in accord to serve as a satisfactory control for the subsequent nitrogen-free period. When the question arises as to the character of a diet which shall be nitrogen-free, we are confronted by the well-nigh impossibility of obtaining one, which shall serve as a palatable and savory substitute for the ordinary mixed diet while containing sufficient calorific value. For many persons the occurrence of nausea under such a diet precludes the possibility of its employment by them. Whether or not this is a psychic phenomenon is still somewhat questionable. The two principal objects to be attained in any such diet are that it be palatable and that by its absence an appetite be aroused, for, in the light of recent work, we can not but appreciate the extreme importance which must be attached to the psychic factors of digestion. These conditions unfortunately are hard to obtain. The usual ingredients of this diet are some form of pure starch, pure saccharose or other sugar and fat in the form of butter or thick cream. This combination has been employed by many investigators and especially by Pfeil,[2] Landergren[3] and by Folin[4]. The latter, referring to arrowroot starch, which is commonly employed, gives it as his opinion that it is free from nitrogen and more palatable than corn or potato starch. The former statement is not strictly true, since nitrogen in small amounts can be detected in most samples of this type of starch. Relative to the degree of palatability of the starches as prepared by semidigestion with diastase (Folin) it can only be stated that it is a choice between evils of somewhat equal intensity. In any case, flavoring of some kind must be added to render it savory, after which it makes little difference what kind of starch has been employed. Without further discussion as to the diet suffice to say that, after personal experience, we decided that for our taste the daily diet most adapted to prolonged general use was the following:

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[1] We are of course well aware that to prepare a diet containing absolutely no nitrogen is well-nigh impossible. The term is constantly employed, however, as significant of the relatively low nitrogen content of the constituents when compared to the ordinary or even the meat-free diet.

[2] *Ztschr. f. physiol. Chem.*, xl, p. 1.

[3] *Skand. Arch. f. Physiol.*, xiv, p. 112.

[4] *Am. Jour. Physiol.*, xiii. p. 66.

Grams.	Calorific value.
250 arrowroot	957.0
140 pure cane sugar	504.4
50 butter	450.0
100 fat in the form of 250 c.c. of 40 per cent. cream	900.0
Sodium chlorid to taste.	2811.4

The whole daily allotment was prepared at one time, but was eaten in approximately three equal parts at the three meal hours during the day. The preparation took place as follows: The arrowroot was thoroughly stirred into 400 c.c. water in which the cane sugar and salt (about 20 gm.) had been previously dissolved. This was poured into a boiling mixture of equal parts of the cream and water and the whole well beaten under constant boiling for 20 minutes. At this point the mixture assumed the character of a blanc mange. The pudding was then flavored with various kinds of extracts and fruits. The presence of small quantities of nitrogen in the berries and fruits thus employed may account for the slight variations in the amount of nitrogen eliminated from day to day; the fluctuations, however, are not sufficient to affect whatever changes may have been noted.

From the thermodynamic standpoint the diet was ample. This fact is particularly evidenced by the rapidity with which the nitrogen elimination diminished during the starch-cream diet. On two of the subjects on the third day, and in the third on the fourth day, there was less than 3 gm. of nitrogen excreted during the 24 hours. These figures approach those of Siven[7] and of Landergren.

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[7] *Skand. Arch. f. Physiol.*, xi, p. 308.

METHODS.

The total nitrogen was estimated by the Kieldahl-Gunning method. The urea was determined by the Mörner-Sjoquist method, with the exception that in the sodium salicylate experiment a total nitrogen determination was made on the ether-alcohol filtrate (after the removal of the ether and alcohol) and from this quantity was subtracted that determined for the ammonia by separate analysis. Ammonia was estimated by the Shaffer method; uric acid according to the Hopkins-Folin method; creatinin by Folin's adaptation of calorimetric readings to Weyl's test. The calorimeter employed was made to order for us by Mr. E. C. Fasoldt, expert mechanician of Albany, N. Y., after designs with modifications according to the sketch by Van Hoogenhuyze and Verploegh.[1] This instrument reads to 0.001 inch (0.0254 mm.). Duplicate readings could easily be made to within 0.126 mm., which corresponds to .015 G. creatinin, according to Folin's calculation, giving results easily within the limits of error.

The inorganic phosphorus pentoxid was determined by titration with uranium nitrate, using potassium ferrocyanid as indicator. The organic phosphorus pentoxid estimation took place as follows: 100 c.c. of urine was evaporated to dryness, fused with sodium hydrate and potassium nitrate and on the fused mass the phosphorus pentoxid determination was made by the ordinary gravimetric method. The difference between this and the inorganic phosphorus pentoxid determination gave the organic phosphorus pentoxid. Total acidity was estimated by titration with sodium hydroxid, employing phenolphthalein with potassium oxalate, as suggested by Folin. Tables 1, 2 and 3 give the figures obtained in the analysis of the purin-free and nitrogen-free periods.

Before we take up the discussion of the main problem it may not be out of place to emphasize some few points which are brought out by the results of the starch-cream diet and also by a comparison of the latter with the purin-free period. In general the figures for creatinin may be considered as confirmatory to a certain degree of Folin's contention that in meat-free diets the elimination of this substance is independent of the amount of nitrogen excreted. No great variations occur in our figures, but they do, however, plainly indicate that the character of the diet

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[1] *Ztschr. f. physiol. Chemie*, xlvi, p. 419.

TABLE 1.—H. C. J.

Date.	Volume in c.c.	Sp. gr. 1.0—	Total Nitrogen, gm.	Per cent of Total Nitrogen as Grams Nitrogen eliminated as					P_2O_5.		Acidity in c.c. $\frac{N}{10}$ Acid. Total.	Remarks.
				Urea.	Ammonia.	Uric Acid.	Creatinin.	Undetermined.	Inorganic, gms.	Organic, gms.		
9	950	28	8.7	87.3 7.61	4.5 .398	1.5 .130	5.4 .443	1.3 .12	1.80	......	....	Purin-free diet.
10	815	25	9.6	89.5 8.55	3.1 .297	1.4 .138	4.7 .460	1.3 .15	2.17	......	....	Purin-free diet.
11	805	26	10.0	89.9 8.99	3.9 .397	1.2 .118	4.6 .464	0.4 -.04	2.14	......	....	Purin-free diet.
17	430	25	4.8	75.2 3.61	6.8 .328	2.8 .133	10.6 .514	4.6 .21	0.93	.077	379.5	Starch-cream diet.
18	810	15	3.7	70.0 2.58	10.3 .382	2.5 .092	12.5 .464	4.7 .18	0.90	.050	216.0	Starch-cream diet.
19	650	15	2.8	58.5 1.64	13.7 .383	2.0 .055	15.7 .449	10.1 .27	0.90	.020	189.0	Starch-cream diet.
20	860	15	2.6	60.3 1.60	11.6 .308	3.9 .102	16.9 .449	7.3 .19	0.87	.077	171.0	Starch-cream diet + alcohol.
21	1115	15	2.4	58.3 1.43	14.0 .343	3.0 .073	19.1 .468	5.6 .14	0.82	.099	145.5	Starch-cream diet + alcohol.

TABLE 2.—K. D. B.

9	1215	26	9.63	86.6 8.34	5.3 .512	1.8 .175	5.48 .526	0.9 0.9	1.84	......	....	Purin-free diet.
10	1200	24	9.24	87.1 8.05	5.3 .486	1.4 .128	5.6 .522	0.6 .6	2.46	......	....	Purin-free diet.
11	1295	14	8.94	86.1 7.70	4.7 .417	1.7 .149	6.1 .551	1.4 .12	2.08	......	....	Purin-free diet.
17	1785	12	4.43	72.4 3.21	11.6 .515	0.52 .023	10.2 .454	5.3 .23	.84	......	161.3	Starch-cream diet.
18	1710	12	3.42	69.1 2.36	12.0 .411	0.35 .012	14.5 .497	4.0 .14	1.00	......	154.8	Starch-cream diet.
19	1700	12	3.28	61.2 2.01	15.7 .516	0.39 .013	14.0 .461	8.7 .28	1.10	......	184.6	Starch-cream diet.
20	2550	05	2.97	62.9 1.87	12.9 .383	0.54 .016	16.6 .494	7.0 .23	1.11	......	88.4	Starch-cream diet + alcohol.
21	2570	05	3.08	66.2 2.04	11.4 .351	1.00 .031	16.1 .497	5.3 .16	.73	......	115.5	Starch-cream diet + alcohol.

TABLE 3.—J. F. R.

9	550	32	9.06	86.2 7.81	4.6 .420	1.7 .157	5.1 .463	2.3 .21	1.83	......	....	Purin-free diet.
10	790	28	11.14	89.5 9.98	3.5 .392	1.2 .139	4.4 .498	1.4 .13	2.25	......	....	Purin-free diet.
11	900	28	9.08	88.8 8.07	3.6 .330	1.8 .162	4.8 .436	1.0 .08	2.76	......	....	Purin-free diet.
17	400	28	6.16	79.0 4.87	5.5 .341	1.8 .114	9.3 .576	4.3 .26	1.03	......	423.0	Starch-cream diet.
18	980	24	4.17	70.9 2.96	8.1 .338	2.3 .099	11.2 .469	7.5 .30	1.09	......	273.0	Starch-cream diet.
19	850	13	2.72	55.9 1.52	13.5 .369	3.3 .090	18.2 .496	9.1 .26	1.07	.098	240.0	Starch-cream diet.
20	825	14	2.52	55.9 1.41	12.9 .327	5.0 .128	19.5 .491	6.7 .17	.82	.410	216.0	Starch-cream diet + alcohol.
21	720	15	2.21	54.3 1.20	14.9 .329	5.4 .120	22.4 .496	3.0 .08	.83	.055	186.0	Starch-cream diet + alcohol.

does exert in some manner a distinct though variable influence on the quantity of creatinin eliminated; further variations in creatinin elimination were also noticed, but these will be discussed later. Averages for the purin-free diet periods in the case of each of the three persons (A, B and C) are: Creatinin, A, 1.23 gm.; B, 1.43 gm.; C, 1.25 gm.; for the starch cream periods, of which there are two each for A and C: A, 1.13 gm. and 1.28 gm.; B, 1.26 gm.; C, 1.38 gm. and 1.33 gm. Considered as a whole, these figures might be regarded as lying within the limits of error. When the results for the individual days are examined it will be seen that only in two instances do the values in one series come within the limits of its comparative series, thus indicating differences which lie outside of the factor of their variability. This condition would tend to throw doubt on the statement made by the same author that the elimination value is constant for each individual, but different for different persons. This we could not confirm. Undoubtedly the explanation for this does not lie primarily in the character of the diet, but in the general condition of the cells of the body (endogenous metabolism) influenced secondarily by the diet, but not dependent directly on its nitrogen. In this sense Folin's ideas perhaps would find confirmation.

The effect of the nitrogen-free diet with its high calorific value is admirably shown when we consider the elimination of urea and ammonia, both in absolute quantities and in their relation to the total nitrogen output. In the purin-free period the percentage of the total nitrogen eliminated as urea varied from 86.2 to 89.9 in the three persons; the ammonia, from 3.1 to 5.3, figures which may be considered to be well within normal limits. The average for the control nitrogen-free period does not indicate as accurate a picture of the change inaugurated by the diet as would an inspection of the individual figures. However, the urea-nitrogen percentage of the total diminished to 55.9 and 79.0 per cent (last day of periods 55.9, 61.2 per cent) and the ammonia increased to 5.5, 15.7 per cent (last day, 13.5, 15.7 per cent). These figures are in complete confirmation of Folin's[4] results. In fact, they apparently answer the question propounded by this author as to the possibility of still further reducing the percentage of urea-nitrogen below the level of 60 per cent found by him. A glance at the figures in the tables will suffice to enable one to answer this interrogation positively. The constancy of the ammonia elimination both in the purin-free and nitrogen-free periods is worthy, perhaps, of some attention.[1] This fact would indicate that under normal conditions a portion of the ammonia output does not stand in any direct proportion to the excretion of urea (endogenous elimination). Superimposed on this constant amount is that eliminated as the result of secondary influences such as diminution in the urea-forming function or acidosis. The effect exerted on the uric acid by the change from purin-free to nitrogen-free diet is equally interesting. The experiments of Burian and Schur[2] and, independently, of Siven and of Pfeil would tend to indicate that the uric acid elimination is independent of the total nitrogen output in purin-free diets. Folin's results stand at variation with this statement, and this author enters into a well-directed discussion as to the probable cause of this discrepancy. He concludes that not all of the uric acid eliminated during the so-called purin-free diet can be considered endogenous. We feel that our results show ample substantiation for this contention. There is a distinct and marked diminution in the absolute quantity of uric acid output during the nitrogen-free diet as compared with the purin-free period. In fact, in two of the three individuals the decrease was out of all proportion to the decrease in the nitrogen elimination, and hence there resulted an actual percentage diminution. The third case reacted similarly to those of Folin, in which there resulted an absolute decrease, but an increase in proportion to total nitrogen. Extremely interesting in connection with a possible explanation of these differences is the fact brought out by Folin that in a one-day change of diet from arrowroot to potatoes the individuals excreted more uric acid than on previous or subsequent days. As Burian and Schur's purin-free diet included potatoes, he suggests that perhaps the so-called purin-free articles of diet are not such in the sense of not causing the formation of purins. An examination of Folin's figures, however, indicates that not only is the uric acid, but also the creatinin and urea increased, and, more important still, the absolute quantity of ammonia markedly diminished so that the percentage output assumes almost that of the normal. If the potato diet merely affected the uric acid and indirectly the total nitrogen output the above explanation might be correct. In the light of the increase in urea and creatinin[1] and decrease in ammonia observed, it would seem as if a more probable explanation would be that the nitrogen content of the potato had simply caused the metabolism to return to the level of a higher nitrogen elimination which is under these conditions always accompanied by lowered percentage ammonia excretion. The basic content of the potato could not suffice to cause this change in the ammonia elimination. We will have occasion to return to this point when the effect of the drugs on the elimination of ammonia and uric acid is discussed. The inorganic phosphates suffered a decrease, while the undetermined nitrogen both increased in absolute quantity and in per cent of total nitrogen.

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[1] Schittenhelm, C. F., and Katzenstein: *Ztschr. f. exp. Path. u. Therap.*, ii, p. 542.

[2] *Arch. f. die Gesammte physiol.*, lxxxvii, p. 239.

We have entered into this somewhat prolonged discussion of our control results mainly that there might be presented clearly the differences which appeared between the purin-free and nitrogen-free diets, placing special emphasis on the uric acid elimination in order that a basis should be established on which changes due to the drugs must be reckoned. Incidentally there has entered the necessity of confirming Folin's results. These we feel have been amplified while the several points become more distinctly drawn by the increased calorific value of the diet.

ACTION OF DRUGS.

A nitrogen-free diet, during which the nitrogen metabolism may be said to be strictly endogenous in character and reduced to its lowest minimum, appeared to us to present the best possible condition for the study of changes induced by the administration of certain agents about the effects of which on the elimination there are differences of opinion. It was hoped to obtain under such circumstances data which might be of service in throwing some light on the factors directly or indirectly implicated in the deranged metabolism.

ALCOHOL.

In view of the etiologic relationship which is thought to exist between alcohol in its various forms and arthritis uratica, it was thought essential to study the effect exerted by this substance on the relationships of the nitrogenous constituents of the urine excreted during the time of a nitrogen-free diet. Within the limits of this paper we can not discuss even in a meager manner the mass of literature, discordant in greatest part, concerning the chemistry of perverted metabolism in gout. It must suffice to confine ourselves to the effect produced by alcohol primarily on uric acid and secondarily on urea, ammonia, creatinin, the inorganic phosphates and the organic phosphorus elimination in the hope of eliciting facts that may throw light on the changes which occur.

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[1] In both of the cases indicated the creatinin elimination on the potato days reached the level of the milk-egg diet.

The results obtained by various investigators in this direction are somewhat discordant and incomplete. The earlier work of Herter and Smith must be disregarded on account of the lack of knowledge at that time of the importance of regulating the diet. Again, all experiments concerning uric acid formation which are carried out on dogs can serve merely as confirmatory evidence, since we are aware of the distinct difference in nuclein metabolism which exists between dogs and man.

Later, the first well-devised experiments were those of Rosemann on a young man unaccustomed to the use of alcohol. His results do not find easy explanation. Suffice to say that 0.78 gm. of uric acid was excreted *per diem* during the 10-day alcohol period, as against 0.82 gm. during the control period. The 1,500 c.c. of 5 per cent alcohol added to the diet evidently not only did not increase the uric acid elimination, but tended to diminish it.

Beebe's carefully conducted experiments next appeared. In most of his experiments the examination of the urine was made hourly; alcohol pure and in its various forms was ingested both with and without food. The diets were rigorously observed, some of them containing purins and some purin-free. His deductions, which have a direct bearing on our topic, are as follows: In one experiment when alcohol (250 c.c. of 20 per cent.) was taken at one dose without food the hourly excretion of uric acid showed no change. A close examination of his figures might justify other conclusions, however. During the course of the experiment the hourly quantity of uric acid diminished from 30 mg. to 20 mg. and for three hours after the ingestion of the alcohol the subject was in a state of narcosis. Although the first hour after alcohol showed a decided decrease (from 31 to 26 mg.) in uric acid excretion, the following three hours averaged more than this (28 mg.). In view of the fact that a decided diminution was taking place in the uric acid output during the day, these figures might well be taken to indicate at least a temporary stoppage of that decline if not a positive increase. This experiment is not convincing. At the same time it must be admitted that Eschenburg[1] came to similar results, although his experiments were not so carefully carried out. On the other hand, Beebe found that both with purin-containing food and with a purin-free diet alcohol increased the elimination of uric acid, but that the increase was the greatest the larger the purin content of the food. In this Eschenburg also agrees. The increase, examined hourly, reached its maximum from 4 to 5 hours after the meal. Since the maximum increase as the result of the ingestion of food also occurs at that time, Beebe considers that additional proof is supplied for his conclusion, from the above experiments, that the increased uric acid excretion after alcohol is due to a disturbed metabolism of the purin constituents of the food.

While we have no results which are exactly comparable to his, the fact that on a nitrogen-free diet there took place a decided increase in the elimination of uric acid during alcohol ingestion must throw some doubt on the theory which Beebe advanced. In the following experiments the diet remained unchanged, but on the first day 300 c.c. of 25 per cent alcohol was taken in 7 doses at two-hour intervals during the day. No effect was noticeable, except that when the administration occurred at the time when the stomach was empty the usual sensation of warmth was felt; on the second day 200 c.c. of cognac containing about 50 per cent alcohol was ingested in 8 aliquot parts at two-hour intervals. This was without narcotic effect of any kind, and the subjects kept about their usual work in the laboratory (Tables 1, 2 and 3). From the figures of the tables, the following effects of alcohol may be readily noticed. Their general discussion appears later. A distinct diuretic effect, most marked in subject B, less so with J, and not noticeable in subject R (unaccustomed to alcohol) occurs. No proteid sparing action can be observed. A definite rise in uric acid excretion takes place (25 to 50 per cent). The elimination of ammonia undergoes a decrease. The creatinin output stands unchanged. There is marked increase in the organic phosphorus.

In our experiments the increased uric acid elimination might either be due first to an increased oxidation of purins of endogenous origin or, second, to an increased formation (synthesis) of uric acid, or perhaps, third, to a diminished oxidation of the uric acid.

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[1] *Münch. med. Wochschr.*, xlvii, p. 2263.

According to the first supposition, the quantity of purin bases eliminated should undergo a diminution in the proportion as they suffered an increased oxidation to uric acid. Unfortunately our determinations of the purin bases during these experiments were not sufficiently satisfactory or complete to warrant their presentation at this time. It can only be stated that no diminution apparently occurred; but we expect to verify this in a later publication. Beebe found an increased output of purin bases coincident with the augmented excretion of uric acid.

In the second supposition, if an increased synthesis occurred, changes should also have taken place in the other nitrogenous constituents or their antecedents which furnished the nitrogen for the synthesis. This did actually appear in that the ammonia elimination both absolutely and in its percentage of the total nitrogen diminished. Here again, our results are in direct opposition to those of Beebe, in which there was a decided increase in the ammonia output. While our periods were not as prolonged as his, still our figures are less variable, and the decrease in the three cases is, respectively, 6, 12 and 29 per cent. To correlate this fact with the increase in uric acid is somewhat difficult; perhaps they represent two distinct processes in no relation to each other. It is well known that the ammonia elimination stands in close relationship to the formation of acids in the organism, its function in part being that of a neutralization agent. Based on this idea, the diminished ammonia elimination would point to a diminished formation of acids from decreased decomposition of proteid or fats in the organism. In this case the diminished ammonia output would stand in no direct relation to the augmented uric-acid output. One noticeable effect due to the alcohol is the undoubted increase in the organic phosphorus elimination which occurred not only with alcohol, but after other agents (colchicum and sodium salicylate), which also increase the uric-acid output. Various attempts have been made to show that increased uric acid or purin elimination was followed by an augmentation in the quantity of inorganic phosphates excreted. This having proven impossible, attention has been turned to the organic phosphorus of the urine.[1] It would seem most plausible that in the formation of purin bodies, especially uric acid, from the nucleoproteid of the cell the phosphoric acid of the nucleic acid component should be eliminated, if not as an inorganic phosphate, perhaps in "organic" form, i. e., as nucleotin phosphoric acid,[1] and not determinable by reaction with uranium nitrate. Our results apparently point to this latter type of production and excretion, and hence in its relation to uric-acid formation the increased elimination would indicate that the augmented uric-acid output was dependent on an increased decomposition of phosphorus containing nuclear material (nucleoproteid, nucleins or nucleic acids) of the cell. In the light of this increased elimination of organic phosphorus pentoxid, the decreased output of ammonia occurring at the same time might be explained, as hinted above, by a diminished formation of acid radicles, perhaps phosphorus pentoxid. The figures in the table do in fact indicate that an actual decrease in the output of phosphorus pentoxid, precipitable with uranium nitrate, did occur.

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[1] Oertel: *Ztschr. f. physiol. Chem.*, xxvi, p 123; also Mandel and Oertel: *N. Y. Univ. Bull. Med. Sci.*, i, p. 165; Symmers: *Jour. of Path. and Bac.*, x, p. 159.

Thirdly, that the increased elimination of uric acid is attributable to a decreased oxidation of this compound in the liver as supposed by Beebe seems hardly probable. At any rate, the results adduced by this author do not seem sufficient to strengthen the supposition. With the exception of the figures presented by him, we know of nothing which would tend to substantiate the deductions. By this it is not intended to imply that the liver may not be one of the seats functionating in the decomposition of uric acid, although this also has not been decisively proven. But it must not be forgotten in this connection that alcohol[2] and other uric acid increasing agents (colchicum, sodium salicylates,[3] etc.) tend to increase the activity of the liver and also its blood supply as shown by their acting as cholagogues. This certainly would speak against the view of an impaired function of this organ.

The creatinin elimination remained unchanged during the alcohol period. This fact would afford evidence against the view that the purins and creatinin have a common origin.[4] Nor could any nitrogen sparing effect be noticed, such as shown by the tables of Beebe. That the nitrogen elimination during the alcohol periods is less than that during the control period, we can not deny, since it is so evident. But a consideration in detail of the individual days in the previous control period will plainly indicate that the nitrogen output was steadily diminishing and, unfortunately, had not reached its lowest level when the administration of the alcohol began. Hence we are more inclined to attribute the decrease noted to a continuation of the fall inaugurated in the previous period than to any effect of the alcohol. Also one of the subjects (R.) was unaccustomed to alcohol, and in his case we should not have expected the appearance of a sparing effect; it is evident, however, that it was just in his case that the most evident decrease occurred. The explanation probably lies in the fact that with the high calorific value of the diet the small amount of energy supplied by the alcohol was insufficient to alter the nitrogen elimination in an amount greater than the daily variation. The decreasing values in the control period just alluded to are also evident in the uric-acid excretion. On this account the increase in uric acid observed is much more marked than the average figures actually show.

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[1] Schmiedeberg: *Arch. f. exp. Path. p. Pharm.*, xliii, p. 57.

[2] Salant: Proc. *Soc. exp. Biol. and Med.*, vol. i, p. 43.

[3] Kionka: *Ztschr. exp. Path. u. Therap.*, ii, p. 9.

[4] Burian: *Zeitschr. f. Physiol. Chem.* xliii. p. 546.

Colchicum and Sodium Salicylate.

As far as we are aware no experiments have been recorded on the effect produced by these drugs on the nitrogenous elimination during a nitrogen-free diet. Many experimenters have considered the action of colchicum on the elimination of uric acid, especially in pathologic conditions, but the diets have been such or the methods employed were of such doubtful accuracy as to render it useless to quote them. The consensus of opinion, as indicated by statements in Cushny's text-book on "Pharmacology," seems to be united, however, in considering that uric-acid elimination is not increased after its administration, and that its use is purely empirical.

Concerning salicylates, the same statements hold true in general, except that the weight of evidence lies emphatically on the side of an increased output of uric acid as the result of their ingestion. Recently, however, Morgenbesser[1] reported experiments conducted on a normal individual, which apparently indicated a difference in the action of these compounds, whether on normal or on pathologic metabolism of uric acid. In a three-day period, during which 30 gm. of sodium salicylate were ingested daily, he noticed an increase in the nitrogen elimination of from 9 to 16 per cent. This increase is made up almost entirely of urea. The uric acid and purin bases were diminished, however.

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[1] *N. Y. Med. Jour.*, 1906, lxxxiii, p. 760.

TABLE 4.—K. D. B.

Date.	Volume in c.c.	Sp. gr. 1.0—	Total Nitrogen, gm.	Per cent of Total Nitrogen as Grams Nitrogen eliminated as: Urea.	Ammonia.	Uric Acid.	Creatinin.	Undetermined.	P₂O₅. Inorganic, gms.	P₂O₅. Organic, gms.	Acidity in c.c. $\frac{N}{10}$ Acid. Total.	Leucocytes.	Remarks.
22	1410	08	2.37	60.3 1.43	13.9 .331	0.68 .016	18.5 .440	6.4 .16	.67	......	115.5	......	Starch-cream diet following alcohol.
23	1725	08	3.03	66.3 2.01	11.0 .334	0.53 .016	14.6 .443	7.5 .23	.78	......	109.8	......	Starch-cream diet + colchicum.
24	1455	08	2.52	60.3 1.52	15.5 .392	2.30 .058	17.2 .435	5.0 .12	.93	......	100.5	......	Starch-cream diet + colchicum.
25	1275	10	7.69	80.7 5.21	6.7 .515	3.5 .274	6.8 .529	2.3 .16	1.42	......	142.5	......	Meat diet.

TABLE 5.—H. C. J.

22	555	20	2.70	64.0 1.73	10.7 .288	1.2 .032	16.6 .448	7.5 .20	.79	.045	147.0	......	Starch-cream diet follow. alcohol.
23	615	21	2.36	59.7 1.41	11.8 .280	1.9 .045	18.4 .436	8.2 .19	.73	.038	145.5	......	Starch-cream diet + colchicum.
24	1005	11	2.39	62.3 1.49	12.0 .287	2.9 .070	16.9 .404	5.9 .14	.92	.099	163.0	......	Starch-cream diet + colchicum.
25	535	23	5.86	78.7 4.61	8.9 .523	2.8 .162	7.8 .464	1.8 .10	.86	......	154.5	......	Meat diet.
31	385	25	4.38	79.5 3.48	5.6 .249	1.3 .059	9.6 .425	4.0 .17	1.03	......	163.0	......	Starch-cream diet.
1	520	22	3.69	72.7 2.68	9.1 .337	1.1 .039	11.3 .420	5.8 .21	.87	......	150.0	5600	Starch-cream diet.
2	575	23	3.14	69.8 2.19	10.0 .313	0.7 .024	13.3 .418	6.2 .20	.74	......	154.5	5340	Starch-cream diet.
3	1300	14	3.36	72.3 2.44	9.8 .331	2.2 .075	12.5 .422	2.3 .08	.80	......	199.5	5560	Starch-cream diet + sodium salic.
4	2000	10	3.05	67.2 2.05	8.9 .272	5.5 .167	13.1 .400	5.3 .16	.73	......	120.0	6730	Starch-cream diet + sodium salic.

TABLE 6.—J. F. R.

22	470	21	2.06	56.3 1.16	15.2 .314	3.2 .066	22.8 .471	2.5 .05	.80	.012	183.5	......	Starch-cream diet following alcohol.
23	1080	18	2.94	65.6 1.93	10.9 .321	4.1 .120	16.7 .496	2.5 .07	1.04	.135	222.0	......	Starch-cream diet + colchicum.
24	1195	09	2.43	57.5 1.40	14.5 .353	2.8 .069	20.2 .492	5.0 .12	1.02	.113	196.5	......	Starch-cream diet + colchicum.
25	825	21	6.89	79.5 5.38	6.8 .475	4.0 .278	8.0 .552	2.7 .20	1.25	......	249.0	......	Meat diet.
31	525	22	5.39	80.0 4.31	6.4 .346	1.9 .103	9.3 .502	2.4 .13	1.16	......	255.0	......	Starch-cream diet.
1	550	23	4.77	77.7 3.71	7.1 .339	2.0 .099	10.3 .495	2.9 .13	.88	.058	258.0	6150	Starch-cream diet.
2	750	22	3.70	71.6 2.65	10.6 .395	1.9 .072	13.4 .495	2.5 .09	1.00	.063	205.5	5340	Starch-cream diet.
3	850	22	3.04	66.1 2.01	13.5 .413	1.4 .043	15.8 .482	3.2 .10	.89	.105	244.5	5560	Starch cream diet + sod. salic.
4	950	20	2.64	61.3 1.62	10.9 .288	4.2 .112	16.3 .431	7.3 .19	.97	.068	261.0	6930	Starch-cream diet + sod. salic.

In our experiments the colchicum was administered in the form of the wine taken on the first day at two-hour intervals, seven doses of 30 m. each. As no typical symptoms occurred, the next day the dose was increased to 40 m. Four such doses were taken, beginning at 8:20 a. m., when at 2 p. m., diarrhea set in; this, however, was counteracted by bismuth subgallate, but later characteristic symptoms, nausea, headache, etc., appeared and the drug was discontinued.

The sodium salicylate was ingested at similar intervals in doses for the first day of 5 gr. dissolved in water; in all, 45 gr. during the day. On the second day 10 gr. and 30 gr. doses were administered, making altogether 110 gr. The ordinary effects of buzzing in the ears and heart-burn, etc., were experienced. Tables 4, 5 and 6 indicate the result obtained by us.

Concisely stated, the figures show that both colchicum and sodium salicylates inaugurated a distinct increase (both absolute and in percentage of total nitrogen) in the output of uric acid probably not accompanied by a diminished purin base excretion. In the case of the salicylate the increase amounted to about 250 per cent. A coincident decrease in the ammonia elimination did not occur in the case of colchicum, but was distinctly evident in both subjects the last day of the sodium salicylate administration. The creatinin elimination also decreased at the same time. The figures are not concordant with reference to the total nitrogen output. With colchicum, two of the three cases showed a rise in the nitrogen elimination, but in one of them the increase did not occur on the day when the output of uric acid was maximum. The salicylate showed less effect, there being but a slight augmentation of nitrogen excretion in one case, and this when the uric-acid elimination was not at its height. We are inclined to believe that these drugs do not effect the elimination of endogenous nitrogen, at any rate not to the extent mentioned in the text-books. That they may cause an impaired internal assimilation of exogenous nitrogen and hence increased elimination, can not be denied. The unknown state of our knowledge concerning the factors which cause the excretion of creatinin under a creatinin-free diet renders a discussion of the results which we obtained somewhat vague and theoretical. The decrease in ammonia nitrogen and creatinin nitrogen observed as the effect of salicylates seemed to be offset by the increase in uric acid nitrogen and undetermined nitrogen. Just in what manner this rearrangement is brought about or its metabolic significance can only be conjectured.

The inorganic phosphorus pentoxid elimination remained unchanged. The fragmentary figures which we present as to the organic phosphorus pentoxid indicate an increase in the elimination. As in our previous discussion of this point in its relation to the increased uric acid output, we feel that additional evidence is added to the view that the augmentation in output is caused by increased production from nuclear material of the cell.

The acidity showed no change; no leucocytosis made its appearance during the administration of salicylates. The foregoing results have been substantiated by similar experiments by Dr. A. T. Laird on patients suffering with gout.[1]

CONCLUSIONS.

1. The elimination of uric acid on a purin-free or nitrogen-free diet is not a constant value for the same individual.

2. There appears to be evidence that the elimination of creatinin may be altered by conditions other than that of the creatinin in the food.

3. Alcohol increases the output of uric acid during a nitrogen-free diet; there occurs a coincident diminution in the elimination of ammonia; the organic phosphorus pentoxid excretion is also increased.

4. Both colchicum and sodium salicylate increase the output of uric acid, along with which takes place an augmented excretion of organic phosphorus pentoxid.

5. These facts seem to indicate that the rise in the uric acid elimination is caused by an increased formation as a result of augmented decomposition of nuclein-containing compounds of the cell.

6. From this it seems reasonable to decide that any agent which tends to cause an increased production of uric acid in the organism and thereby to increase its amount in the blood, must be contraindicated in those conditions where there exists a tendency for a deposition of urates to occur (gout). Probably the temporary beneficial effects of salicylates and colchicum observed clinically are the results of some secondary action possessed by them. That no permanent benefit results must be due to the fact that they are contraindicated.

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[1] Results to be published later by Dr. Laird.

EXPERIMENTAL MYOCARDITIS; A STUDY OF THE HISTOLOGICAL CHANGES FOLLOWING INTRAVENOUS INJECTIONS OF ADRENALIN.*

By RICHARD M. PEARCE, M. D.

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PLATE I.

During a recent investigation[1] by Dr. Stanton and myself of the lesions occurring in the aorta of the rabbit as the result of repeated injections of adrenalin, the heart muscle, in the few instances in which it was examined, was seen not infrequently to be the seat of very definite degenerative lesions and occasionally also of proliferative changes. The association of such conditions with an experimental vascular lesion suggested the possibility of producing experimentally a chronic myocarditis analogous to that seen not infrequently in man in connection with grave arterial disease. As the material at hand was insufficient for a comprehensive study a second series of investigations was inaugurated. In these an attempt has been made to study the sequence of the changes and to determine to what extent they are due to the direct action of adrenalin and to what extent secondary to the arterial lesions. Few of the investigators who have produced vascular lesions with adrenalin have described the associated myocardial changes. Fischer[2] mentions the occurrence of necrotic and fibrous changes and, rarely, calcification. K. Ziegler,[3] in a series of eight animals, found changes very similar to those hereinafter detailed.

Methods.—These were practically the same as in the earlier experiments by Dr. Stanton and myself, except that the initial dose was placed at one-tenth cubic centimetre, and rapidly raised to five-tenths and occasionally higher. All injections were made into the ear vein, and usually on alternate days. As previous experiments had shown that ten to twelve injections of adrenalin were sufficient to produce well marked arterial lesions, the injections in this series with a few exceptions were thus limited and the animals were then allowed to remain without further treatment for periods varying from one to three weeks. Thus the animals which survived the treatment represent an average injection period of twenty-four days, and a total elapse of from twenty-seven to forty-five days, a sufficient time, as indicated by the few preliminary observations, for the development of proliferative lesions in the myocardium. The animals dying during the course of the injections furnished sufficient material for the study of early degenerative changes.

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The histological methods were limited to the use of Scharlach R for frozen sections, and of hæmatoxylin and eosin and Mallory's connective tissue stain for material hardened in Zenker's fluid and imbedded in paraffin.

Results.—Thirty-six rabbits were injected. These may be divided into two groups: the first group including fourteen animals which died during the period of injection, and the second group, twenty-two animals, which received from seven to fifteen injections and were killed at various intervals thereafter. The first group represents animals receiving from one to five injections, of which none died later than the tenth day. All animals dying in this stage succumb apparently to circulatory and respiratory disturbance and present at autopsy acute dilatation of the heart, œdema and congestion of the lungs, and occasionally hæmorrhages from the serous and mucous membranes or in the interior of organs. No macroscopic lesions of the aorta are demonstrable. When death follows the injection within a few minutes the cardial dilatation, especially after the fourth or fifth injection, is extreme. Under such circumstances the heart loses much of its conical shape; the apex is more or less rounded and the over-distended auricles project laterally and greatly broaden the base. The left ventricle is very anæmic, and its pale almost bloodless substance is in sharp contrast to the blue-black color of the thin walled auricles.

Degenerative Changes.—The heart muscle of two of three rabbits dying within a few minutes after a single injection shows a well marked œdema causing more or less separation of the muscle fibres: in the third animal the œdema is slight. In all three the muscle fibres show irregular swellings, and the striations are somewhat indistinct. In one, multiple fractures of more or less homogeneous fibres are frequently seen, but as these conditions could not be found in either of the other hearts, they were considered as probably artifacts.

But one animal died after two injections. This death occurred on the fourth day, thirty-six hours after the second injection. The œdema of the myocardium is so great as to cause wide separation of the muscle fibres in many areas. In some of these areas the fibres have lost their striations and are very granular. A few small areas of intense œdema take a diffuse blue stain similar to myxomatous tissue.

Three animals died after three injections. The notes on one of these follow:

Rabbit No. 25.—Male, weight 1670 grammes. The initial dose was one-tenth cubic centimetre of a one to one-thousand solution of adrenalin injected into the ear vein. On the following day the dose was raised to two-tenths and after an interval of two days it was repeated. The animal was found dead seventeen hours after the last injection. At autopsy œdema and congestion of the lungs and extreme dilatation of the heart are present. Histologically the heart reveals focal areas of most intense œdema. These occur not only in the wall of the ventricle but also in the papillary muscles. Crossing these areas are strands of connective tissue in the midst of which fragments of heart muscle may occasionally be seen. Some of these fragments stain well while others are merely shadows of fibres in the midst of the finely granular coagulated serum. Some have ragged irregular ends pointing definitely to displacement by fracture. Elsewhere the fibres are widely separated by a serous fluid, are very granular, have swollen nuclei, stain lightly with eosin, and have but indistinct striations. On cross section many of the fibres show a clear zone about the nucleus, evidently a perinuclear œdema. Occasionally, bundles of fibres appear as if torn across, the space between being filled with serum. The branching of the fibres is brought out well by the œdema. Swollen hyaline fibres are not infrequent. The large blood vessels are widely distended; the capillaries on the other hand are not prominent. No lesions are seen in the walls of the blood vessels.

In a second animal of this period which received three injections of one-tenth cubic centimetre the œdema was not so prominent, but on the other hand more extensive granular and hyaline degeneration of the fibres was present. After the fourth injection one animal died and after the fifth, six. These last represent the period of greatest mortality as well as the gravest degenerative lesions. All animals dying at this time showed extreme dilatation of the heart and histologically, in addition to the changes just described, a severe granular and hyaline transformation with more or less necrosis and disorganization. This condition is illustrated by the following protocol:

Rabbit No. 6.—Male, weight 1720 grammes. On September 26, 29, and 30 one-tenth cubic centimetre of adrenalin solution was injected into the ear vein; on October 2 and 3, two-tenths. The animal died during the night of October 3. Upon post-mortem examination the heart was found to be dilated, the left ventricle pale and bloodless, and the lungs œdematous; the other organs were normal. Sections from three levels of the heart show general œdema and extreme disintegration of the muscle fibres. On both cross and longitudinal section the latter are seen to be irregularly swollen, granular, without striation, and not infrequently hyaline. The nuclei are swollen and frequently surrounded by a zone of œdema. In many fibres with extensive vacuolization of the protoplasm the nucleus does not stain. About such fibres small accumulations of mononuclear leucocytes are occasionally present and in some instances foci of epithelioid cells. In areas of extreme degeneration the outlines of the muscle fibres on cross section are indistinct and the picture is that of a uniformly granular mass with regularly placed lightly staining chromatic rings. These various changes affect the papillary muscles also. No changes in the vessels of the heart are demonstrable. Histological examination of the aorta is negative.

In other animals of this period the degenerative changes in the heart were of the same general character though varying more or less in degree. In two, a slight diffuse growth of connective tissue between the muscle fibres occurred.

Attempts to demonstrate fat in frozen sections of formalin hardened material treated with Scharlach R and counterstained by hæmatoxylin were uniformly negative. This method, however, revealed, in a few hearts, isolated fibres or small groups of fibres taking a diffuse yellow stain. These were more or less hyaline, and without nuclei; they however occurred in close relation to other similar fibres which did not thus react. This reaction has not as far as I am aware been previously described and its significance is not apparent.

The lesions in these hearts are due, manifestly, either to the direct toxic action of adrenalin upon the heart-muscle or to mechanical disturbances of the circulation caused by the effect of adrenalin on the vascular mechanism. They cannot be secondary to alterations in the walls of the large vessels, for in this series none of the animals exhibited macroscopic lesions of the aorta and in but three were degenerative changes evident microscopically.

Proliferative Changes.—Of the twenty-two animals surviving seven to fifteen injections, all but three showed degenerative changes in the myocardium, though seldom of the severe grade observed in the above descriptions. In twelve, more or less definite new connective tissue formation was evident. This new tissue was present, in some hearts, as focal accumulations of fine connective tissue about individual hyaline or granular fibres or about small groups of such fibres. In others a diffuse arrangement of new tissue was demonstrable in considerable areas of the myocardium, and in two cases a very severe and diffuse fibrous myocarditis existed. The new tissue as a rule was most abundant about the blood vessels but had no relation to the sub-epicardial tissue or to the endocardium. It was very prominent in the papillary muscles. All parts of the ventricle suffered, though if any difference existed, the lesions were more severe at the apex. Focal accumulations of leucocytes were not prominent in the more chronic lesions, though occasionally present in the earlier conditions. When present these were usually of the lymphoid cell type. No suppuration or other evidence of infection was seen at any time; the lesion apparently was a pure connective tissue proliferation following degeneration of muscle fibres. The following protocol is that of the most advanced lesion observed:

RABBIT No. 22.—Male, weight 1685 grammes. During a period of eleven days seven injections of adrenalin varying in amount from one-tenth to eight-tenths cubic centimetre were given (total amount five and two-tenths cubic centimetres). The animal was killed by chloroform five days after the last injection.

Autopsy.—Weight 1650 grammes. A small amount of clear serous fluid is found in the peritoneal and pleural cavities. The heart is large and firm; the walls of the left ventricle are distinctly thickened; the auricles are dilated. The entire circumference of the aorta at its origin is the seat of closely massed, depressed, round or oval, calcified areas which form a complete ring about the vessel and extend irregularly into the sinuses of Valsalva and along the ascending portion of the aorta for a distance of one and two-tenths centimetres. The orifices of the coronary arteries, in the natural position of the aorta, are entirely obscured but by pressure on the heart substance their presence is indicated by the escape of minute points of blood. These lesions cause considerable deformity of the vessel. A few isolated plaques of similar appearance are scattered elsewhere in the aorta and a considerable number are grouped about the origin of the cœliac axis.

Histology.—Sections through the entire ventricle from base to apex show extreme degeneration of muscle fibres and a new formation of connective tissue diffusely arranged, for the most part, but with here and there focal areas in which the muscle fibres are entirely absent. The muscle fibres as a rule are swollen, vacuolated, and exceedingly granular, though some are atrophied. Fibres with irregular constriction and swelling and more or less hyaline transformation are not uncommon. The nuclei are distorted, stain poorly, and frequently are entirely absent. In some fibres the nucleus is contracted and surrounded by a clear zone; in other fibres the nucleus is greatly swollen. The connective tissue is

PLATE I.

To Illustrate Dr. Pearce's Article "Experimental Myocarditis."

Albany Medical Annals, January, 1907.

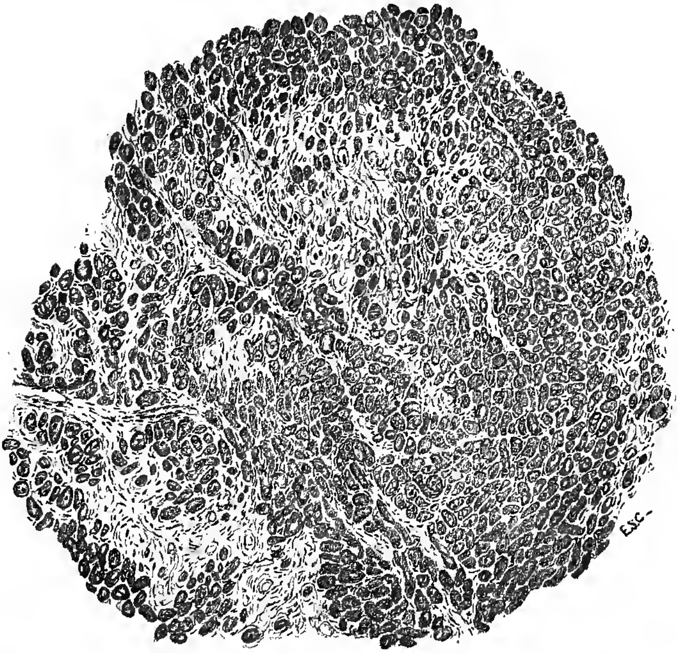

FIG. 1.—Fibrous myocarditis with more or less focal arrangement of the new tissue. Rabbit No. 22; see description in text.

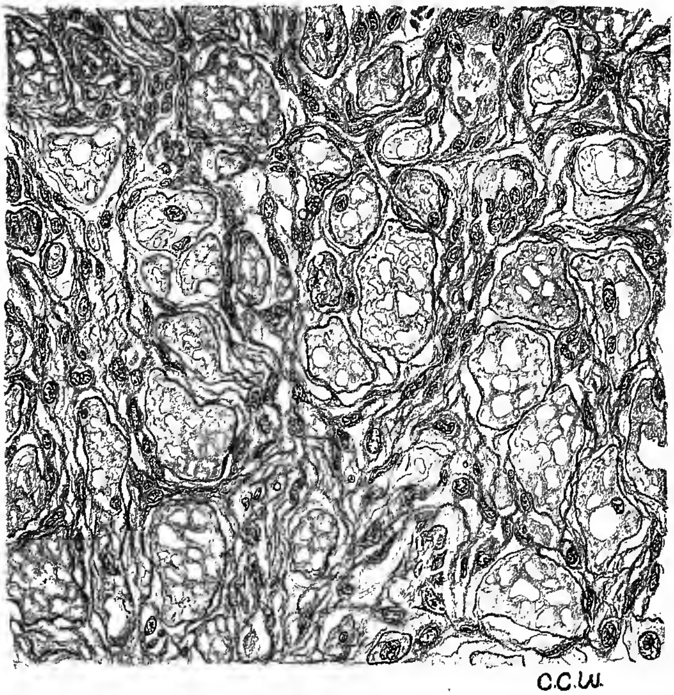

FIG. 2.—Higher magnification of a different portion of the same section showing the character of the muscle degeneration and also a moderately diffuse increase of connective tissue.

more abundant in the mid and inner portions of the ventricle and but slight beneath the pericardium and in the papillary muscles. The focal areas are more numerous at the apex of the ventricle and towards the endocardial surface. The connective tissue is very loose and œdematous. Between the elongated wavy vesicular nuclei is considerable intercellular substance practically free of lymphoid cells. While the arrangement of the new tissue is in general diffuse it is frequently more abundant about the blood vessels. In the focal areas the fibrillated character of the new tissue is very evident. The walls of the blood vessels show no change. Sections stained by Mallory's connective tissue method show everywhere between the muscle fibres a more or less well marked blue reticulum, while the focal areas take a deep stain relieved only by the deep red of fragments of hyaline fibres. The methods for demonstrating elastic tissue show a diffuse increase of fine elastic fibrils in the denser areas of connective tissue; they reveal no changes in the blood vessels.

Control Observations.—Although the literature treating of various experimental lesions of the myocardium of the rabbit contains no references to the occurrence of degenerative and proliferative changes in the hearts of apparently normal rabbits, it seemed advisable to determine definitely this point. As the sacrifice of a series of normal rabbits appeared undesirable the sections of heart muscle from a large number of animals injected with various organs and fluids of the dog during the past few years, in the course of several investigations of cytolysins, were utilized. A careful study of this material failed to reveal fibrous changes and showed few degenerative lesions. The latter were of slight degree and never of the type occurring after the administration of adrenalin.

Mode of Action of Adrenalin.—The association of a severe fibrous myocarditis with vascular lesions involving the orifices of the coronary arteries, as in the experiment given above in detail, suggests that the latter condition must have some causal relation to the myocardial changes. Indeed in the early part of the investigation it was thought that such a relation would eventually be demonstrated. Such, however, does not appear to be the case, for in one instance a myocarditis of equally severe type developed in the entire absence of lesions in the aorta. Moreover in six of the twelve animals exhibiting changes in the myocardium no lesions of the aorta were present, and in three of the remainder the lesions were but slight. The fibrous changes in the myocardium would appear therefore to be independent of the vascular lesions and not analogous to the myocarditis associated with arterial disease in man.

Other possible explanations are based on a direct toxic action of adrenalin on the heart muscle, or an indirect action through the mechanical disturbances of the circulation which it causes. Although the physiological action of adrenalin on smooth muscle is well known we have no knowledge of its toxic action on the various types of muscle cells. Degenerative lesions in the parenchymatous cells and in muscle cells other than those of the heart and aorta are rarely seen, and it seems improbable that the toxic principle of adrenalin, if it exists, should be so selective as to affect only the muscle cells of the heart and the smooth muscle of the aorta and its larger branches. Indeed the limitation of degenerative lesions to the heart and larger blood vessels, and their practical absence in all other tissues, speak against any toxic action and point to an influence of a mechanical nature affecting these structures alone.

The action of adrenalin in constricting the arterioles with consequent increase in blood pressure is well known. This increase of blood pressure is alone not sufficient to explain the lesions, for if it were, we would expect the vascular changes due to adrenalin to be more general. But it is admissible to conceive of a temporary ischæmia of terminal vascular territories, due to the direct action of the drug upon the smooth muscle cells of the coronary arterioles, which lasts a sufficient length of time to cause some interference with the nutrition of the affected areas. From physiological experiments this period would appear to continue about ten to fifteen minutes. If to this we add the increased contractile effort of the heart necessary to overcome the greatly augmented intravascular tension, we have factors sufficient to explain the degenerative lesions of the early experiments. The heart muscle under conditions of poor nutrition is pushed to its extreme power and dilatation results with injury of single fibres or groups of fibres. This injury is due in part to nutritive and in part to mechanical disturbance. That the dilatation is extreme, that the muscle is anæmic, and that serious alterations of the fibres are associated with this condition after but a single injection of adrenalin has been repeatedly demonstrated during the course of this investigation.

Practically the same explanation was advanced by Dr. Stanton and myself to explain the necrosis in the lesions of the aorta due to adrenalin. K. Ziegler's explanation of the vascular lesions is also very similar. He points out that the inner and middle portions of the media of the aorta, the usual seat of necrosis, is the part of the vessel most scantily supplied by the vaso-vasorum and therefore most susceptible to necrosis at the time of vascular spasm and local anæmia.

Comparison with Other Experimental Lesions of the Myocardium.—The degenerative changes due to adrenalin do not conform in all respects to those caused by other agents used experimentally. The hyaline and granular changes in the muscle fibres, the alterations in striation, and the slight accumulations of lymphoid cells are similar to those found by various investigators (Comba,[4] Welch and Flexner,[5] and Mollard and Regaud[6]) who have studied the effect of diphtheria toxin on the heart muscle. On the other hand they differ in the absence of fatty changes, in the extreme œdema of the interstitial tissue, and in the disorganization of the fibres. In the same way also they differ from the lesions produced by Welch[7] in his experimental study of the effect of high temperature and from those produced by Ribbert[8] with staphylococcus pyogenes aureus, by Charrin[9] with bacillus pyocyaneus, by Tallquist[10] with streptococcus pyogenes, by Björksten[11] with various bacteria or their toxins, and by Flexner[12] with ricin and abrin.

With the exception of the slight focal increase of connective tissue described by Charrin, Comba, and Mollard and Regaud, as a rare result of repeated injections of bacterial toxins, the only form of fibrous myocarditis mentioned in the literature of experimental lesions of the heart is that following ligation of the coronary arteries. The histological changes following such ligation have been described by Kolster, Porter, and Baumgarten[13]. The last, in his very detailed description, states that by the fourteenth day the new connective tissue had largely replaced the widespread areas of anæmic necrosis. This is of interest in connection with the lesions above described, in that the most marked connective tissue proliferation occurred in a rabbit killed sixteen days after the first injection.

Relation to Lesions in Man.—No definite comparisons can be made. The animals with acute degeneration of the myocardium and extreme dilatation of the heart which die suddenly after the fourth or fifth injection represent a condition apparently similar to that occasionally seen in man, where unusual strain causes sudden death due to an acute dilatation of a heart previously injured by some toxic agent or disturbance of nutrition. The later fibrous lesions have no analogy to the commoner chronic forms of myocarditis in man associated with arteriosclerosis or following known toxic conditions. That some of the more unusual forms of fibrous myocarditis in man which are difficult of explanation may be due to circulatory disturbances of the same general nature as those caused by adrenalin injections in the rabbit cannot be denied. It is to these only that the results of this experimental investigation appear to have any relation.

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A NOTE ON THE PRODUCTION OF VASCULAR LESIONS IN THE RABBIT BY SINGLE INJECTIONS OF ADRENALIN.*

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The many publications which have followed Josué's demonstration of the power of adrenalin to produce degenerative changes in the rabbit's aorta have added much to our knowledge of the degenerative, infiltrative and repair processes which may occur in blood vessels, but unfortunately, from the point of view of comparative pathology, the value of this method of experimentation has been lessened by the failure to produce lesions entirely analogous to those of arteriosclerosis in man, the condition which it most closely resembles, and further by the absence of an adequate explanation of the manner in which adrenalin acts to produce such lesions.

This method, however, is so full of promise that it seemed advisable to continue the investigations[1] carried on in this laboratory, during the past two years, in the hope of producing, by varying the conditions of the experiment, lesions more closely resembling those of arteriosclerosis in man and at the same time to study by exact physiological methods the action of adrenalin. These studies are as yet incomplete and it is our intention in this communication to refer only to the lesions caused by single injections of adrenalin.

That repeated frequent injections of adrenalin are necessary to the production of experimental vascular lesions appears to be the opinion of all who have used it. Loeb and Githens[2] have stated that lapse of time is of more importance than frequency

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[1] R. M. Pearce and E. McD. Stanton, "Experimental Arteriosclerosis," *Journal of Exper. Med.*, 1906, viii, 74; R. M. Pearce, "Experimental Myocarditis: A Study of the Histological Changes Following the Intravenous Injection of Adrenalin," Ibid. 1906, viii, 400.

[2] "The Effect of Experimental Conditions in the Vascular Lesions Produced by Adrenalin," *Amer. Jour. of the Med. Sci.*, 1905, cxxx, 658.

of injections or size of dose, and although they alone appear to have noted this fact they did not materially limit the number of injections in their experiments.

Our attempt to produce lesions by single injections was mainly for the purpose of testing the theory offered by Pearce and Stanton and later supported by the former in his study of experimental myocarditis due to adrenalin. This was, briefly, that in both the aorta and the myocardium the primary condition is a localized anemia, due to the direct action of adrenalin on the arterioles of areas not readily supplied by collateral circulation. To this factor is added the influence of the strain thrown upon these poorly nourished parts during the height of the increase in blood pressure, an influence sufficient presumably to cause permanent injury. If lesions could be produced by single injections of adrenalin this theory would be strengthened and that of direct toxic action weakened.

As it had been previously shown that necrotic foci were present in the aortas of animals receiving four and five injections, three groups of animals were given respectively one, two and three intravenous injections of ½ to 1½ minims of a 1:1000 solution of adrenalin (Parke, Davis & Co.). Although lesions were produced in animals receiving two and three injections they became of little importance in view of the very positive results following single injections. Of ten animals in the latter series four died within a few minutes after injection; of the remaining six, one of which died at the end of seven days and five of which were killed after sixty-five to seventy days, all showed very definite vascular lesions. The protocols of these experiments may be briefly summarized as follows:

Experiment 13.—A full-grown rabbit received in the ear vein on December 9th, one half a minim of a 1:1000 solution of adrenalin. No ill effect was noticed after recovery from the initial disturbance. On December 16th, the animal was found dead. Postmortem examination revealed edema of the subcutaneous tissues, minute hemorrhages in the intestinal serosa and about 20 c.c. of slightly blood-tinged fluid, in the peritoneal cavity, but no increase of fluid in pericardial or pleural cavities. The heart was somewhat dilated and its muscle pale. Beneath the epicardium were numerous punctate hemorrhages. The aorta throughout the thoracic portions presented a peculiar wrinkled appearance without well-defined thickening or change in color. The other organs were not noteworthy.

Histological examination of the aorta at different levels revealed an extensive and diffuse degeneration of the media with more or less complete necrosis of the muscle cells and a straightening and fusion of the elastic fibres with a few angular bends. About two-thirds of the circumference of the vessel was involved and transversely the middle third of the media. In the heart muscle were focal areas of degeneration with slight increase of connective tissue and accumulation of lymphoid cells.

EXPERIMENT 17.—Rabbit weighing 1100 grams injected on January 4th with one half minim. Chloroformed March 14th; weight 1710 grams. Upon postmortem examination 75 c.c. of clear watery fluid were found in the peritoneal cavity. The aorta from its origin to celiac axis presented numerous irregular, calcified placques varying in size from 0.2 to 1.5 cm. in diameter. The other organs showed no changes. Upon histological examination the aortic lesions were those of degeneration and calcification.

EXPERIMENT 20.—Rabbit weighing 1920 grams injected on January 9th, with one minimum of adrenalin. Killed March 14th; weight 2120 grams. Postmortem examination revealed no lesions except in the aorta which from origin to bifuraction was dotted with oval and linear elevated areas of thickening and calcification. The areas were larger and more abundant in the ascending portion. Well-marked thickening was present about the orifices of the coronary arteries. Histological examination showed the usual picture of necrosis and calcification.

EXPERIMENT 21.—Rabbit weighing 2230 grams received on January 9th, one and one-half minims of adrenalin and was chloroformed on March 15th. At autopsy no changes were found except in the aorta which presented just above the celiac axis a single irregular area of a calcification 0.8 cm. in diameter. Upon histological examination very extensive repair was evident about the calcified area and especially in the subintimal tissues.

EXPERIMENT 22.—A rabbit weighing 1860 grams was injected on January 9th, with one and one-half minims of adrenalin. Chloroformed on March 15th; weight 1910 grams. In the aorta just above celiac axis are two calcified patches, the larger of which measures 0.5 cm. in diameter. The histological picture was that of calcification with no repair.

EXPERIMENT 23.—Rabbit, 1950 grams in weight, was injected January 9th. Killed March 14th; weight, 2700 grams. In the upper portion of abdominal aorta is one small wrinkled thickening 0.3 mm. in diameter which presents histologically, the picture of calcification.

These results, while they offer no explanation of the mode of action of adrenalin in producing vascular lesions, simplify the mode of investigation in that the problem is limited to the study of the effect of single injections, and comparisons may sharply be drawn between lesions so produced and similar lesions caused by prolonged administration of other substances, as nicotin, digalen and barium chloride.

It is evident, however, that in view of these results the theory of direct toxic action is hardly tenable, while that which recognizes a combination of vaso-vasorum disturbance, local anemia and vascular strain is greatly strengthened.

A FURTHER STUDY OF THE EXPERIMENTAL PRODUCTION OF LIVER NECROSES BY THE INJECTION OF HEMAGGLUTINATIVE SERA.*

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The observations herein detailed are supplemental to an earlier communication,[1] in which was described the power of the hemagglutinins contained in various cytolytic immune sera to form red blood corpuscle thrombi, and also the relation of the latter to necroses of the liver. In a later study[2] of the repair following lesions of the liver so produced, abundant confirmation of the earlier work was afforded. These observations, however, have not been generally accepted as conclusive. Though no other explanation of the necrosis has been offered, the masses of fused corpuscles in and about the necrotic tissue are still described by some investigators as artifacts, or as the consequence of post-mortem changes. It seems advisable, therefore, to present various control observations which offer very conclusive evidence in support of the views expressed in my first communication.

Without going into detail the lesions under consideration may be described as hyalin necroses, the position and extent of which vary according to the amount of serum[3] administered. Small doses cause focal lesions more or less isolated and irregularly distributed; large doses produce a diffuse necrosis which spares only the tissue about the larger portal spaces. The lesions are found only in the superficial portions of the liver, seldom in the deeper portions. In animals dying before the appearance of necrosis an intense congestion exists. Under such circumstances, the vessels are found upon microscopic examination to be distended by red blood corpuscles so closely massed as to present oftentimes a homogeneous appearance. The coalescence of red cells is very evident in the portal veins, while in the capillaries the occlusion leads to a distension so great that the columns of liver cells are more or less obscured. This congestion is less evident about the larger portal spaces. Endothelial cells, fibrin and bacteria do not enter into the formation of the thrombotic

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masses. An occasional leucocyte or endothelial cell may be seen, but as a rule these are absent.

Such observations have led me to conclude that the cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal vein by fused masses of red cells. To the effect of this obstruction, essentially a thrombosis, is added the pressure exerted by the perivascular edema and the over-filled bile capillaries. In parts of the liver midway between the larger portal spaces these factors are sufficient to overcome the pressure in the capillaries from the hepatic artery, and necrosis results; the cells in the neighborhood of the larger portal spaces, on the other hand, are preserved through a better blood supply, dependent, presumably, upon the greater arterial pressure in this region.

Although the rôle of the hemagglutinin in producing these necroses seems to me to be well established, it is necessary, as nearly all cytotoxic sera have manifold activities, to control by experiment other possibilities. Of these the most important are the action of the toxic products of hemolysis and the direct action upon the liver cells of some toxic substance in the injected serum.[4] This last seems improbable, as a recent study[5] of a number of cytotoxic sera, including hepatotoxin, has shown that the necroses do not result from somatogenic cytotoxins unless the serum has a high hemagglutinative power. Similarly sera of great hemolytic power do not cause necrosis unless the agglutinative power also is great. Moreover, it was shown that a serum of great agglutinative but no hemolytic power—that prepared by injecting bile—produces necroses as widespread and characteristic as those caused by sera of the highest hemolytic power. Nevertheless, as the sera which produce necrosis are, with the exception of bile serum, those which have great hemolytic activity, it seemed advisable to carry out various control experiments to determine whether or not this hemolysis had any share in the development of the necroses. It is to this phase of the subject that this communication is devoted.

Methods.—All attempts to remove from a serum its hemolytic activity, leaving only the agglutinative power, have been unsuccessful. The removal of this power by heating, so valuable in experiments in the test-tube, is not applicable to animal experiments, as the serum is activated by the complement of the injected animal. The action of chemicals and digestants affects the agglutinin as well as the hemolysin. The same is true of changes in serum due to lapse of time after withdrawal, and also of the serum of animals which are not bled for several months after the final injection. Even the positive results obtained by bile serum might be considered inconclusive owing to the possibility of a natural dissolution of the red cells after agglutination with the escape of toxic substances capable of causing necrosis. It became necessary, therefore, to determine what lesions might be produced in the liver by injecting the products of hemolysis and by producing experimental hemolysis by various substances having little or no agglutinative power. If such substances produced no necroses the theory of agglutinative thrombi would, in a negative way, be greatly strengthened.

Incidentally, numerous vital injections have been made to demonstrate that the masses of red cells do cause a complete obstruction of the vessels during life not only in areas of complete necrosis, but also at various periods preceding necrosis.

Experiments with the Products of Hemolysis.—I. To produce in the living animal a more or less continuous blood destruction, rabbits have been injected daily with normal dog's serum. Although this serum causes in the test-tube an agglutination of rabbit's red cells, this agglutination is very fine and disappears very rapidly as the result of the powerful hemolytic action which it possesses. Four rabbits were injected. Each received an initial dose of one cubic centimeter of serum in an ear vein, and the dose was gradually increased according to the condition of the animal. Two died on the twenty-first and twenty-second days respectively, the daily dose having reached ten cubic centimeters. The other two died on the thirty-sixth day, the dose having been suddenly increased from fifteen to twenty cubic centimeters. All showed the characteristic lesions of experimental anemia, *i. e.,* large swollen spleen, hyperplasia and edema of the lymph nodes, a diffuse dark red appearance of the bone-marrow, fatty changes in the liver, heart, and kidneys, petechial hemorrhages of the pericardium and lungs, edema of the lungs, and a hydremic state of the blood with lax clotting. The serum of one animal bled just before death was quite deeply colored by hemoglobin. In none of these animals could focal lesions of the liver be seen macroscopically. Histologically, all showed extreme granular and vacuolar degeneration, and one extreme fatty transformation. In none were areas of hyalin necrosis found.

II. In a similar way dogs received intravenous and intraperitoneal injections of horse serum which, though powerfully hemolytic for dog's corpuscles, is but slightly hemagglutinative. Injections of this serum in doses varying from 1:800[6] to 1:280, and repeated every three to four days until four injections had been made, failed to produce focal lesions of the liver, although the presence of albumin in the urine and fatty changes in the kidney indicated the toxic action of the serum.

III. For the study of the effect of blood disintegration by a known chemical body toluylendiamin[7] was selected. This substance produces in the test-tube a slow hemolysis of the red cells, but no agglutination other than the mechanical massing of the cells after standing for several hours. Administered to the dog by the mouth it causes an exquisite experimental anemia accompanied by icterus. Six dogs received toluylendiamin with their food. Of these one was given a dose sufficient to cause death within twenty-four hours. The others were given small doses almost daily and sacrificed after one, three, five, six and eight weeks. The usual procedure was to begin with one-tenth of a gram and increase the dose very gradually to one-half a gram. When it was desired to terminate the experiment a fatal dose was given. Animals surviving a week or longer become emaciated and jaundiced, and albumin and bile appear in the urine. The blood[8] picture and the changes in the bone marrow, spleen and lymph nodes are those characteristic of experimental anemia.

The liver is of a greenish yellow color mottled with large, irregular yellowish or brownish areas. Its surface is smooth or finely granular, its substance firm and one section of a uniform greenish yellow color with smooth glistening appearance. In five of the animals of this group no trace of hyalin necroses similar to those caused by cytotoxic immune sera could be found upon either gross or microscopic examination. In the liver of the animal killed in the sixth week were found irregular focal areas of granular necrosis and extensive infiltration of leucocytes with the formation of a fibrin network. In these areas, which in no way resembled the necroses due to agglutinative thrombi, were masses of bacteria. They must therefore be considered as due to infection and not to the products of blood destruction. All the livers exhibited extreme granular and vacuolar degeneration amounting, practically, in some instances to necrosis of individual cells. The bile capillaries were greatly engorged with bile and could be followed easily both without and within the cells. No accumulated masses of red cells could be seen in the capillaries.

IV. Although the above experiments appeared to prove conclusively that the products of extensive hemolysis occurring in the living animal are not capable of causing necrosis in the liver, it seemed advisable to determine the effect of such products produced artificially. For this purpose eight dogs received injections of laked blood. The solution of hemoglobin was prepared from normal dog's blood by the addition of hemolytic immune sera. The first experiments were extremely unsatisfactory, for it was found that even after standing forty-eight hours the laked blood contained a sufficient excess of agglutinin to agglutinate red cells in the test-tube, and as it produced liver necrosis in injected animals it was impossible to draw any conclusions from such experiments. However, by centrifugalizing the fresh mixture of cells and serum after standing in ice for a half hour it was possible to remove in the supernatant fluid the excess of immune serum. Then, by diluting with salt solution and adding normal dog's serum to the residue, the hemolysin fixed to the agglutinated cells was able to complete the hemolysis at room temperature. The fluid thus procured was a rich solution of hemoglobin with little or no agglutinative power. The injection of this fluid, after standing one to four days, into the mesenteric veins in doses as high as sixty cubic centimeters (1:100), caused fatty changes in the kidney but no necrosis of the liver.

The Production of Necroses by the Injection of Agglutinated Masses of Red Cells.—In the earlier experiments on this subject several attempts were made to demonstrate the mechanical nature of the occlusion of the capillaries by injecting small amounts, five to ten cubic centimeters, of agglutinated corpuscles into the mesenteric veins. These experiments have been repeated with larger doses. Large amounts of blood agglutinated by an immune serum were allowed to stand in the cold for ten to fifteen minutes and then washed hastily by centrifugalizing in two changes of salt solution to remove the excess of serum. Fifty to eighty cubic centimeters of such a mixture have been injected directly into the mesenteric veins of dogs weighing five to seven kilos. In these animals hemoglobinuria occurs and necroses are found in the liver, but not comparable in number or extent to those produced by the serum itself. Those which do occur are, however, typical hyalin necroses. The occurrence of hemoglobinuria in these animals would at first glance appear to vitiate the experiment as it is possible to conceive of the necroses being due to the products of hemolysis and not to mechanical obstruction of the capillaries. Control experiments, however, demonstrated that the injection of the same amounts of normal defibrinated blood into the mesenteric veins causes hemoglobinuria of equal degree but no lesions in the liver. It therefore seems fairly conclusive that the necroses following the injection of clumped corpuscles are due to mechanical obstruction, and that in the production of these necroses the products of the associated hemolysis play no part.

Demonstration, by Vital Injections, of the Occclusion of the Liver Capillaries.—In order to demonstrate that the masses of fused red corpuscles do actually occlude the blood vessels, a series of nine animals, which had previously received hemagglutinative sera, have been injected with carmine during life. For this purpose an ammoniacal solution of carmine, prepared according to the formula of Chrzonszczewsky,[9] was prepared and injected as nearly as possible under natural conditions of pressure.

This preparation penetrates readily the capillary system of all organs and is of especial value in demonstrating occlusion of the capillaries of the liver. With animals under ether anesthesia, ten to twenty cubic centimeters of ammoniacal camine were injected into the hepatic artery, into the veins of the mesentery, and into the femoral vein at various periods after the injection of the agglutinative serum. For detailed study frozen sections of formalin-hardened material stained in hematoxylin have given the best results. In no instance have pigment granules been found in the vessels of the necrotic foci, though they are seen closely packed in the vessels about such areas. The lesions in all these animals were of the diffuse type and there was considerable evidence to indicate that not only the capillaries, but branches of the portal system of considerable size, were occluded. Similar injections made four hours after the introduction of the agglutinative serum penetrate the superficial portions of the liver to but a slight extent and very irregularly, whereas under normal circumstances such injection produces a diffuse impregnation. It seems conclusively proven, therefore, that the fused masses of corpuscles cause a mechanical obstruction to the circulation.

No attempt has been made in connection with these injection experiments, mainly because the necrotic lesions were so diffuse, to determine the relation of the smaller focal lesions to the vascular systems of the lobule. Considerable evidence is at hand, however, to indicate that the immunity to necrosis of the tissue immediately about the larger portal spaces, a condition constantly seen in the diffuse lesions, is apparently due to the influence of arterial pressure. Opie[10] has recently shown by injection experiments that the greater pressure of the arterial blood supply in the periphery of the liver lobule is sufficient to keep this portion of the lobule practically free from injected particles of foreign material, thus explaining the relative infrequency of necrotic lesions in this area. It appears plausible that the same theory applied to the blood supply of the tissue about the portal spaces would explain the immunity of these areas to necrosis. All evidence indicates that the cause of the necrosis is an obstructive congestion of the capillaries and the smaller branches of the portal veins by fused corpuscles. The mechanical pressure exerted by the perivascular edema and the distended bile capillaries probably aids the occurrence of necroses by neutralizing, in part at least, the pressure in the capillaries derived from smaller branches of the hepatic artery. The necrosis occurs uniformly in those portions of the liver in which no large vessels are present. In portions in which the latter are present, as the neighborhood of the portal spaces, the arterial pressure is sufficient to preserve the circulation in their immediate neighborhood, while the tissue at a distance is destroyed. Only thus is it possible to explain the normal tissue in the midst of large necrotic areas. The same difference in pressure may explain also the greater extent of the necrosis at the periphery of the liver.

Conclusion.—Whether or not red blood corpuscle thrombi may be concerned in the focal necrotic lesions of man, a question which has been discussed elsewhere,[11] it would appear to be definitely established that such thrombi do occur in the experimental lesions caused by sera possessing hemagglutinative power and that, aided perhaps by the associated perivascular edema and the engorgement of the bile capillaries, they produce necroses of the liver. That the capillaries of such areas are actually occluded by fused red cells is demonstrated by the experiments here described, as is also the inability of the products of hemolysis to produce such necroses.

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REGENERATIVE CHANGES IN THE LIVER:

A STUDY OF EXPERIMENTAL LESIONS IN THE DOG.*

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PLATE II.

Elsewhere[1] I have described a form of experimental cirrhosis which in its nature is essentially a repair of extensive but more or less irregularly arranged necroses produced by the action of hemagglutinative sera. To this account the present communication is more or less supplemental in that it deals with some of the more important of the finer details of the regenerative

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process, which, for the sake of brevity, were merely outlined in the earlier communication.

The reparative process to be described is of peculiar interest in that it follows definite necrotic lesions produced by an agent reaching the liver through the circulation and not those caused by direct mechanical injury. For this reason, and also because of the resemblance of the early necrotic lesions to acute yellow atrophy and of the later reparative process to cirrhosis, a comparison with the regenerative processes in the liver of man is possible.

Our knowledge of the regenerative changes in the liver is based mainly on the studies of the repair following mechanical injuries and that occurring in acute yellow atrophy and, to a lesser extent, in cirrhosis of the liver. The principal experimental studies[2] since the introduction of aseptic methods and the development of our knowledge of indirect cell division are those of Podwyssozki,[3] Ponfick,[4] and v. Meister.[5] A comprehensive review of the reparative process in acute yellow atrophy may be obtained from the writings of Meder,[6] Marchand,[7] Stroebe,[8] Barbacci,[9] and MacCallum,[10] while the regenerative changes in cirrhosis, first emphasized by Kretz,[11] have since been studied by MacCallum[12] and Kelly.[13]

Podwyssozki, who has made the most comprehensive study of the repair of wounds of the liver produced in various ways, concludes that small losses of substance are repaired, without the formation of fibrous tissue, by proliferation of the liver cells and the cells of the small bile ducts. In more serious injuries in addition to such proliferation a more or less abundant formation of connective tissue occurs. In his studies he used the rat, cat, rabbit and guinea-pig. The formation of new liver cells by mitosis begins after twenty to forty-eight hours and mitotic figures are very abundant by the fourth to the seventh day. Mitoses are also seen in endothelial and connective tissue cells and in Kupffer's cells. The newly formed liver cells are usually large and pale and of round or oval shape. The bile ducts, especially the interlobular, proliferate freely and from them new liver cells may develop directly or they may form large, irregular sprouts in which multinucleated masses of cells appear and from which new liver cells separate. Podwyssozki emphasizes the similarity of the repair of liver cells in pathological conditions to their embryonic development.

Ponfick's experiments, which were repeated by v. Meister, demonstrate that after extirpation of large portions, three-quarters to four-fifths, of the liver of the rabbit a hyperplasia of the remaining substance causes a restoration of the liver to its original size. This proliferation, which is characterized by the formation of lobules of unusual size, is a condition analogous apparently to the vicarious hypertrophy of paired or multiple organs and is due almost entirely to a regeneration of liver cells. Mitoses were first observed after forty-five to seventy-two hours and soon became very abundant. Large, pale, finely-granular cells, often with two nuclei, were very numerous and apparently represent newly formed cells. In the bile ducts and blood vessels also was seen evidence of proliferation, though mitotic figures could not be readily demonstrated.

The so-called adenomatous nodules ("multiple knotige hyperplasie") described by many investigators, and studied especially by Marchand and Barbacci in connection with acute yellow atrophy and cirrhosis, may be considered as the result of a hyperplasia comparable to that produced experimentally by Ponfick and v. Meister. A similar hypertrophy of massive character has been observed by Ponfick[14] in association with echinococcus cyst.

Practically all who have studied the repair process in acute yellow atrophy are in accord concerning regeneration by mitosis of surviving liver cells, but some difference of opinion exists in regard to the solid and tubular cell-strands usually described as newly-formed or pseudo bile ducts. All recent investigators have abandoned the idea that these structures are atrophied rows of liver cells and consider them as sprouts from the small interlobular bile ducts growing into the necrotic lobule. By a gradual transformation of the cells of such sprouts true functioning liver cells are formed. Marchand, however, states that similar structures may also be formed by the proliferation and fusion of the true liver cells in small islands of liver substance which have escaped the general destruction. This latter view Stroebe considers unproven and MacCallum in the one case which he studied was not able to demonstrate this form of proliferation.

The recent studies of regenerative changes in cirrhosis of the liver were undoubtedly suggested by Kretz's statement that this disease is the result of successive processes of repair following repeated focal degenerations of the parenchyma. These studies treat of changes in the size, shape and internal arrangement of the lobule, of its altered blood supply, and of the origin and appearance of the newly-formed cells. In general, the proliferation is similar to that in acute yellow atophy, but, owing to the chronicity of the lesion as seen at autopsy, mitotic figures are rarely found in the parenchymatous cells. The new formation of such cells, however, is indicated by the occurrence among cells of the usual appearance of large, clear, round, plump cells with two or more nuclei and devoid of fat and pigment. What has been said of the newly-formed bile ducts in acute yellow atrophy holds for the similar structures found in cirrhosis.

The present study is based on material from the livers of sixteen dogs representing periods varying from thirty-eight hours to thirty-six days after the injection of the serum. As the larger portion of the animals died during the first week, it is possible to present an accurate account of the sequence of reparative changes to the end of the seventh day. The late changes are also well represented by those animals which survived the acute disturbance. The middle period, however, is not well represented.

The degree of repair has been found to vary considerably at any given period. This is particularly true of the group of five animals representing the period of forty-eight to sixty hours. This difference appears to be dependent in part upon the extent of necrosis and in part upon the general condition and age of the animal. It has been observed, not infrequently, in animals not included in this series that when extensive necrosis of the liver was associated with severe general disturbances, indicated by marked hemoglobinuria and exhaustion, no repair was evident even in those animals surviving to the end of the second day. These various influences have been emphasized by Podwyssozki, who found that mitoses are most abundant when the conditions of nutrition are best. Thus he found mitosis to be delayed in starved animals, after considerable loss of blood and in old animals. In the latter they may fail to appear, as may they also in the neighborhood of suppuration. They are very seldom seen at the margin of areas of complete necrosis.

The primary necrotic lesion may be described as follows: After twenty-four to forty-eight hours the liver presents a uniformly mottled appearance; fine, irregular, yellowish brown or grayish yellow, non-elevated areas being sharply separated from deeply congested or occasionally even hemorrhagic areas. On section the brownish portions have a distinct hyaline appearance. The superficial portions of the liver are uniformly more extensively involved than are the deeper portions, though in some of the small lobes the necrosis may be quite general. Histologically, the necrosis, which is hyaline in character, may involve all portions of the liver tissue except circular areas of varying size in the immediate neighborhood of the larger portal spaces.

In the necrotic areas the destruction, as far as the hepatic cells are concerned, is uniform and complete; the cells of the capillaries may, however, persist. A narrow ring of liver cells with vacuolated protoplasm and pyknotic nuclei separates, as a rule, the necrotic from the normal tissue. Leucocytic infiltration may or may not be present. The capillaries of the necrotic tissue are widely dilated and tightly packed with swollen and distorted red blood corpuscles which may occur in masses or may retain distinct outlines. In the congested portal veins, on the other hand, the fusion is quite constant, the plugs for the greater part having a distinctly hyaline appearance. The perivascular spaces of the capillaries are distended with serum, and the bile passages of all sizes are, as a rule, dilated and engorged with bile.

The earliest evidence of repair, as indicated by karyokinesis of parenchymatous cells, is seen in the liver of an animal which died exactly thirty-eight hours after injection. The necrosis in this instance is very diffuse and accompanied by slight leucocytic infiltration. The destruction of liver as well as endothelial cells in the affected areas is complete. Between the completely necrotic cells and the normal cells is seen a rim of cells two or three deep in which the cell structure is more or less preserved; in these the nuclei are visible but the cell protoplasm is very granular and contains many vacuoles. It is noteworthy that mitoses are not found in such cells but only in the well preserved cells beyond (see Fig. 1). They are very few in number and are found only after prolonged search. This agrees with Podwyssozki's observation that mitoses occur only in perfect cells at a distance from the necrosis. There is some evidence, however, as will be shown later, that the nuclei of apparently degenerated cells, at the edge of the necrosis, may divide by direct division to form multinucleated protoplasmic masses. There is no evidence at this period of proliferation of the endothelial or connective tissue cells or of the cells of the bile ducts.

The period from forty-eight to sixty hours is represented by material from five animals. In these the repair is of the same general character but differs somewhat in degree. Aside from the mitoses of liver cells, which are more abundant, the most striking change is the proliferation of the cells of the supporting framework. The necrotic foci are, on all sides, separated more or less from the normal liver cells by a zone of closely massed newly-formed endothelial cells (see Fig. 2). Proliferation of the same cells occurs in the persisting capillary framework in the midst of the necrosis. The nuclei of these cells, although distinctly vesicular in character, are rich in chromatin and stain deeply. The protoplasm as a rule cannot be distinguished but it may be seen as a faint ring; when distinctly evident it takes a bluish tinge with hematoxylin. Although mitotic figures in such cells are seldom seen the above characteristics indicate a rapid proliferation. Not infrequently at the periphery of the lobule several of these newly-formed endothelial cells surround, in a ring-like manner, hyaline fragments of necrotic cells and simulate in appearance multinucleated cells into which, as will be shown later, many of the cells develop. Occasionally a stray leucocyte is seen in a necrotic cell. Phagocytic activity on the part of single cells within the necrotic focus is indicated by the occasional inclusion of a red blood corpuscle or fragments of necrotic liver cells. A very definite phagocytosis is also evident in the endothelial cells and especially in the Kupffer cells of the capillaries in the immediately adjacent normal liver. Here ten or twenty compressed and poorly staining blood corpuscles may be seen in a single endothelial cell. It is possible that some of these cells may have migrated from the spleen, where they are also very abundant, but the majority are definitely attached to the walls of the interlobular capillaries. In the endothelial cells definite mitotic figures, which can be readily distinguished from those in liver cells, are occasionally seen. They are, however, in proportion to the amount of proliferation, very few in number. Mitoses in liver cells are easily found, but always at a distance from the necrosis. They are never found in the vacuolated cells at the periphery, though between such the proliferation of endothelial cells is most active.

The picture of the third day is that of more advanced replacement of the necrotic cells by young endothelial and connective tissue cells. In many small areas these cells have more or less obscured the hyaline fragments of liver cells. Mitotic figures are more numerous in both liver and endothelial cells and for the first time are seen the large, pale oval or round liver cells described by Podwyssozki, Ponfick, and v. Meister. There is also evident an increase of chromatin in the nuclei of the liver cells. This occurs as a stippling due to numerous closely packed dots and granules which stain deeply and is suggestive of a premitotic activity.

During the fourth, fifth, sixth, and seventh days, the repair progresses with great rapidity but shows few new features. The bulk of the necrotic tissue is gradually replaced by the rapidly proliferating cells. Here and there, however, a few isolated necrotic hyaline masses, usually surrounded by very definite multinucleated cells of endothelial origin, may be seen. Mitotic figures in liver, endothelial and connective tissue cells are readily recognized; in the liver cells they are very abundant, three or four occurring sometimes in a single field of a high power lens. This rapid formation of liver cells occurs not only at the periphery but may, by the fourth day, be seen also in the midst of the destroyed area. Intercellular fibrillæ in the new tissue, first recognizable on the fourth day, rapidly increase and are very definite by the seventh day. Lymphoid cell infiltration first becomes prominent at this period and persists to a moderate extent in the later lesions. Such infiltration, however, is more abundant in the portal spaces, where there is also a proliferation of connective tissue, than in the repair about the necrotic areas. The leucocytic infiltration remains slight.

Despite the most careful study it has been impossible at this stage to determine anything definite concerning the proliferation of the small bile ducts. Not infrequently cells arranged in a circular or longitudinal manner and closely resembling newly-formed bile ducts have been seen. These have no relation to adjacent bile channels and no definite lumen. They closely resemble, however, the processes which Marchand described in yellow atrophy as arising from isolated groups of liver cells and assuming the appearance of pseudo-bile ducts. That they are such appears to be very probable, but absolute demonstration is lacking as it is not possible, even in serial sections, to differentiate in the closely packed mass of proliferating endothelial and connective tissue cells between them and other newly-formed structures. As will be shown later, however, the proliferation described by Marchand can be definitely demonstrated in the more advanced repair and it is possible that the ill-defined structures here described (fifth day) represent the earliest stages of this process.

Of the lesions beyond the seventh day, some on account of the small areas involved in the primary necrosis are unfortunately of little value in studying the intermediate stages of repair. In all, however, there is a very clear picture of the gradual transformation of the young granulation tissue into a very definite connective tissue and of the slow replacement of the latter tissue by newly-formed liver cells, but no new features are presented. In one (eleventh day) endothelial cells in which red blood cells are frequently seen are very numerous; in another (twenty-fifth day) lymphoid and plasma cells, usually present in but small numbers, are very abundant in and about the portal spaces.

The lesions of these intermediate stages, as well as the minute necroses of earlier periods, have been studied carefully to determine whether small areas of necrosis may be repaired by proliferation of liver cells alone without the formation of new connective tissue. Without going into detail it may be stated that such repair, except in minute areas involving but a few cells, has not been noted. In small areas the new formation of liver cells may be so abundant that the appearance may be that of simple hyperplasia of the parenchyma, but by careful study and the use of special stains a new formation of the supporting tissue above that necessary for simple restitution can always be determined. There is, on the other hand, very definite evidence, based upon a comparative study of late lesions of varying extent, that the superfluous connective tissue may be reduced to a minimum when the full development of the new liver cells is reached. Moreover, it can be definitely stated that in the smaller necroses a new formation of bile ducts does not occur; such proliferation takes place apparently only after the destruction of large areas of liver tissue.

The most advanced stage of repair occurring in this series was seen in an animal killed on the thirty-sixth day. The condition present, essentially a cirrhosis, may be described in a general way as a replacement of very extensive necrotic acreas by broad bands of very vascular connective tissue. In and about the new tissue important changes in the liver cells, as well as an excessive formation of new bile ducts, are seen. The liver cells outside of the zone of new tissue are compactly arranged, often irregular in shape and, at the extreme edge of the reactive process, even misshapen. The majority stain normally, but some are swollen and pale with a stippling of the nucleus. Mitotic figures may still be seen in such cells but they are widely scattered. Between these more nearly normal liver cells and the new fibrous tissue is a narrow margin in which fragments of necrotic liver cells still persist. Into this zone from the periphery project large multinucleated liver cells very irregular in shape. Similar cells, with oftentimes ten to fifteen deeply staining nuclei, surround fragments of necrotic cells. Some of these giant cells are in continuity with the strands of normal liver cells, while others are entirely isolated. Such cells may contain four or five hyaline particles which they apparently englobe and disintegrate. These multinucleated masses are essentially foreign body giant cells and though a few of the smaller cells are certainly of endothelial origin the majority appear to be altered liver cells. The protoplasm, which is large in amount, is characteristic of that of the liver cell in every way and, moreover, these cells not infrequently may be seen in direct continuity with strands of liver cells of normal appearance. Isolated giant cells of similar structure but without inclusions are also seen. The material enclosed is in greater part hyaline necrotic fragments of liver cells, but consists also, as determined by micro-chemical tests, of calcified material, occurring as smooth, almost colorless disks. Between these cells a fine connective tissue penetrates, but the great bulk of this zone is made up of giant cells. Similar cells are also seen in the midst of the denser fibrous tissue, sometimes occurring singly, but more frequently in connection with isolated islands of liver tissue.

A careful study of these cells leads to but one conclusion. They are altered liver cells which have developed as the result of an irregular type of nuclear division and which have acquired phagocytic powers which allow them to englobe and destroy necrotic material. There is a possibility that they may be formed by the fusion of several liver cells surrounding necrotic particles, but the occurrence of isolated multinucleated cells without inclusions indicate that such an explanation is not applicable to all these masses (see Fig. 3).

These cells are entirely different from the multinucleated structures formed by the advancing sprout of a new bile as described by Podwyssozki and have not, as far as I can determine, been previously described. McPhedran and MacCallum[15] in their account of the histology of acute yellow atrophy in man, picture somewhat similar structures, but in their description refer to them as cells of the bile ducts. They also describe both endothelial and hepatic cells containing inclusions, but not the multinucleated type of liver cell about necrotic fragments.

Proliferation of the bile ducts while most evident in the new tissue is seen also in the adjacent normal liver. In the latter location, from the canals of medium size, a solid process of newly-formed cells may not infrequently force its way between the normal liver cells and penetrate the zone of multinucleated cells. Oftentimes these strands, which are never canalized, show a division into terminal sprouts composed of conglomerate masses of cells resembling in a rough way giant cells.

Within the new connective tissue new bile ducts are very numerous. In serial sections these may sometimes be seen to have a connection with normal ducts, but more frequently they have no such connection and appear to be the results of the proliferation of persisting fragments of canals which had escaped the primary necrosis. For the most part they are solid processes with irregular swollen branchings or sprouts. Many of these budding processes have on cross section, as has been noted by Podwyssozki, the appearance of giant cells.

Those which have a distinct lumen are usually widely dilated and are either empty or contain a few leucocytes or desquamated cells. Such are usually irregular and tortuous with one or more solid branching processes. In form and structure the cells of which they are composed are intermediate between the true liver cell and the epithelium of the normal bile duct (see Fig. 4). They are usually irregular, or polyhedral in shape, though often oval but never cylindrical. They have a large amount of protoplasm which tends to stain lightly with eosin and closely resembles that of the liver cell. In the solid masses the protoplasm is not so evident. The nuclei are round or oval and, as a rule, vesicular. That these strucures are truly newly-formed is shown by the presence of mitotic figures which though not numerous may be found without great difficulty. In the older portions of the solid processes, as well as in the distinctly tubular structures, not infrequently may be found single cells much larger than the others and with protoplasm very similar to that of the fully developed liver cell. Similar cells of varying size may also be seen in the adjacent connective tissue either as isolated cells or, more rarely, attached to the new bile duct by a thin thread of protoplasm. Such pictures indicate conclusively that liver cells are formed from these structures. The formation of new liver cells from the terminal budding process I have not observed, though it is very probable, as Podwyssozki states, that they may eventually become isolated and be transformed into liver cells. At the stage here studied such transformation has, however, not been seen.

In addition to these processes, concerning the origin of which from preëxisting bile ducts there can be no question, other cell strands of very similar structure which are formed with equal certainty by a proliferation of liver cells are occasionally seen. These are always connected, with the normal liver substance at the periphery or with small islands of liver cells persisting in the center of the new tissue. They occur as closely massed double rows of cells or as groups of cells, usually with budding processes, but never canalized. The cells of which they are composed are similar to those of the solid processes arising from persisting bile ducts and from such processes they cannot be distinguished in their terminal portions; but upon tracing them to their origin they are found to be connected with true liver cells. The transition of the liver cells is gradual and all stages can be traced (see Fig. 3). The point of most abrupt change is usually at the narrowest part of the strand. That these structures may later become canalized is possible, but it seems more probable that they represent rapidly growing cells which later develop into typical liver cells. Such transformation, however, has not been observed. That these strands are not the result of compression of liver cells is shown by the fact that the most active growth is in the distal portion and in the midst, as a rule, of necrotic cells or newly-formed fibrous tissue. These structures are apparently very similar to those seen by Marchand in acute yellow atrophy of the liver.

SUMMARY.

In the necroses of the dog's liver, due to the injection of hemagglutinative sera, the first evidence of repair is the occurrence after thirty-eight hours of mitotic figures in the liver cells. At the end of the second day these have greatly increased and a considerable proliferation of endothelial cells has occurred in and about the necrotic areas. These last tend to encapsulate the necrotic cell fragments. From the third to the seventh day these processes advance, and with the formation of a young granulation tissue, the necrotic areas are largely replaced. While there is some evidence that areas of necrosis involving only a few cells may be repaired by proliferation of liver cells, without the formation of connective tissue, in all areas of appreciable size the latter is a prominent feature. Later, however, as the liver cells increase they replace the connective tissue to great extent. The coarser bands, however, remain. Throughout the entire process of repair the great power of the liver cells to increase by indirect division is the most striking feature. In the late stages of the repair of extensive necrosis many multinucleated liver cells, most of which surround fragments of necrotic cells, may be seen between the normal liver and the dense bands of new tissue. Here are seen also numerous giant liver cells without inclusions. New bile ducts formed from the uninjured larger ducts or from persisting fragments of the smaller canals, aid, by a transformation of their cells into liver cells, in the restitution of the liver parenchyma. The formation of new ducts and the transformation of their epithelium into liver cells occurs, however, only when large areas of liver substances are destroyed. Other cell strands, of the general appearance of new bile ducts, are formed to a slight extent by the direct proliferation of liver cells.

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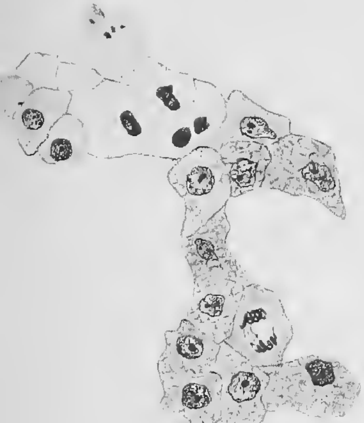

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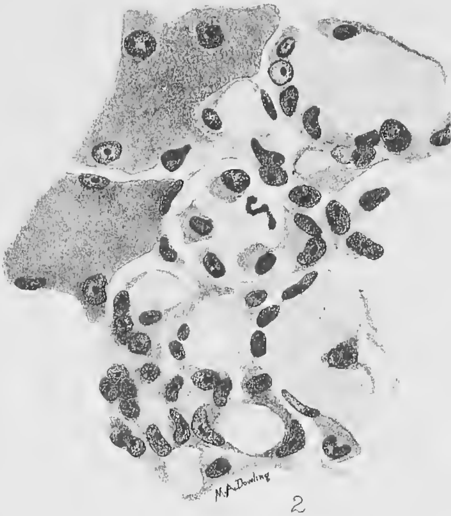

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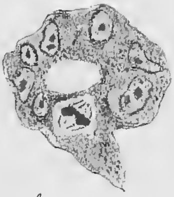

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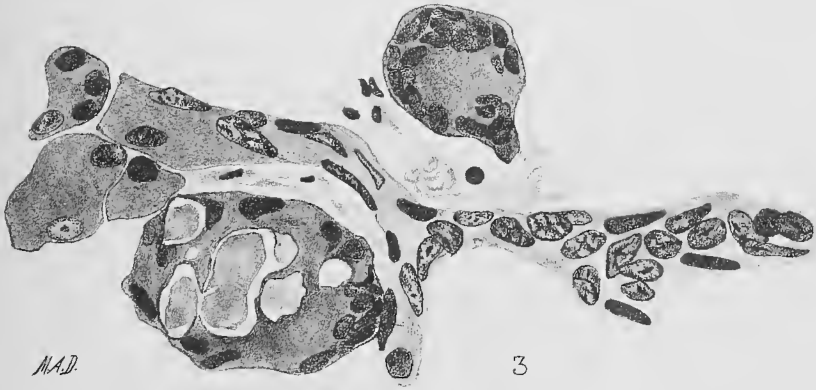

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EXPLANATION OF PLATE II.

Fig. 1. Mitotic figure in a liver cell in the neighborhood of a necrotic area. Thirty-eight hours. 4 oc., 1/12 obj., Leitz.

Fig. 2. Edge of necrotic area showing proliferation of endothelial cells and tendency of latter to encapsulate necrotic cell fragments. In the center is a necrotic cell containing a polymorphonuclear leucocyte. Sixty hours. 4 oc., 7 obj., Leitz.

Fig. 3. Solid process of cells formed by proliferation of liver cells and resembling a branching non-canalized newly-formed bile duct. Below is a multinucleated liver cell inclosing necrotic cell fragments; above is a similar giant cell without inclusions. Thirty-six days. 4 oc., 7 obj., Leitz.

Fig. 4. A newly-formed bile duct in which may be seen a mitotic figure and cells of a type intermediate between true liver cells and the epithelium of the normal bile duct. Thirty-six days. 4 oc., 1/12 obj., Leitz.

LIVER NECROSIS AND VENOUS THROMBOSIS IN HORSES ACTIVELY IMMUNIZED WITH DIPHTHERIA AND TETANUS TOXINS AND WITH STREPTOCOCCI AND THEIR PRODUCTS.*

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PLATE III.

Our search of the literature dealing with the anatomical and histological findings in man or animals dead of diphtheria, tetanus, or streptococcus infections, either natural or artificial, has failed to reveal to us definite records of the conditions similar to those which we are about to describe.†

Law in his extensive work on veterinary medicine gives no descriptions of liver necrosis in the horse exactly comparable to the condition in our series. However, from the statements in his chapter on " Hepatic Hemorrhage and Rupture " we gather the impression that various degenerations of liver cells and subsequent traumatic hemorrhage and rupture of the capsule are far more common in the horse than in man. From his pathological and clinical descriptions the usual cases of hemorrhage and rupture are undoubtedly much milder than those in our horses, as the latter rarely live over ten minutes after the onset of symptoms, while he gives five hours to five days as the period of duration.

Klitine[1] calls attention to fatty degenerations of the liver cells of guinea-pigs, the subjects of chronic experimental diphtheria. Dzierzowsky[2] also mentions the occurrence of fatty degeneration of the livers of horses which have been used in diphtheria antitoxin production.

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*Read at the Sixth Annual Meeting of the American Association of Pathologists and Bacteriologists held at Baltimore May 18, 1906. Published in *Jour. Infect. Diseases*, 1906, iii, 619.

†That liver necroses have been frequently found in horses, the subjects of diphtheria antitoxin production, is no secret to many of those in charge of laboratories where such work is carried on, but no description of this condition has been published as far as we have been able to learn.

[1] *Arch. d. Sci. Biol.* (St. Petersburg), 1900, viii, 2.

[2] *Ibid.* 1902, ix, 293.

Pettit and Girard[1] found complete necrosis of the spleen in a horse used in the production of antiplague serum.

We have to report the finding at autopsy of more or less diffuse necrosis of the liver, or thrombosis of some of the branches of the portal or splenic veins or of the pulmonary artery, either alone or in combination, in twelve horses. These animals had been subjected to repeated subcutaneous injections of the artificially produced toxins of the diphtheria or the tetanus bacillus, or of the various preparations of living or dead cultures, or of suspensions of dysentery bacilli or streptococci. In this series there are seven horses treated with diphtheria toxin, two with tetanus, two with streptococcus, and one with dysentery. A horse treated with diphtheria toxin and killed because of its crippled condition is added to the series for purposes of comparison, as its organs were found to be normal. (See Table 1.)

Superficial postmortem examinations were made of the first three diphtheria horses, and incomplete autopsies, in that no special search for thrombosis was made, on the second three horses in the series. (See Table 1.)

TABLE 1.

SHOWING AUTOPSY FINDINGS RELATING TO NECROSIS AND THROMBOSIS.*

HORSE	SERVICE.					LIVER.		THROMBOSIS OF VEINS.		
	Disease.	Duration Yrs.	Mos.	Sudden Death.	Killed.	Necrosis.	Rupture.	Liver.	Spleen.	Pulmonary Artery.
11....	Diphtheria	1	11	+		Diffuse	+	?	?	?
17....	"	2	1	+		"	+	?	?	?
28....	"	2		+		"	+	?	?	?
36....	Dysentery..		11	+		"	+	?	?	?
37....	Streptococcus	1	9	+		"	+	?	?	?
38....	"	1	9½	+		"	+	?	?	?
21....	Tetanus	3	3	+		"	+	+	+	—
29....	"	3	7	+		"	+	+	—	+
59....	Diphtheria		8		+†	—	—	+	—	—
57....	"		4		+†	—	—	—	—	+
43....	"	2	2	+		Diffuse	+	+	+	—
50....	"	1	7	+		Localized	—	—	—	—
56....	"	1	5		+†	—	—	—	—	—

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[1] *Compt. rend. de la Soc. de Biol.*, 1905, lviii. 272.

*The horses reported upon in this series include all those which have died, or have been killed, after a year and a half of service under the various treatments, since the observations were started.

†Horses 59 and 57 were killed because they were in such a disturbed state that it was impossible to control them. Horse 56 was hardly able to walk on account of the nearly immovable condition of the joints of its legs, and as its serum was of no value it was killed as a matter of economy. Its tissues were normal.

As we have not been fortunate enough to be present when any of the horses died from the effects of hemorrhage and rupture of the liver, we are unable to give a detailed clinical picture of the symptoms preceding death in these cases. The general conditions as described by an attendant are as follows: The animals are apparently in their usual condition. They may have recently eaten a normal meal. Attention is first attracted to them by a rapid noisy breathing. The animal exhibits signs of collapse, and shortly falls to the floor. The breathing becomes very labored and the animal struggles. This stage is followed by a rapid and progressive loss of power, and death ensues. The whole course may not last over ten minutes.

At autopsy the peritoneal cavity contains a very large amount of fluid blood or serum and clots. The liver is usually very soft and friable, and is handled with difficulty. The capsule presents one or more ruptures, and at such places the liver substance is broken up into stringy fragments, interspersed with blood clots. (See Figure 1.)

Our attention was first called to the occurrence of thrombosis in association with diffuse necrosis of the liver by the findings at the autopsy of Horse 21, which occurred April 9, 1905. As is shown in Table 1, this animal had been in active service for the production of tetanus antitoxin for a period of over three years, and was in apparent excellent physical condition when she died in the manner already described. As the protocol of this animal gives a fairly representative picture of the conditions found in the other horses in the series, it will be given in full.

On opening the abdomen a large amount of bloody fluid escapes and many light red clots. The intestines are distended. The glands of the mesentery in the ileocolic region are enlarged and soft. The liver for the most part presents a yellowish-gray color; within the right lobe an encapsulated hemorrhagic mass. On section it is found that the entire liver is necrotic, presenting a grayish color and a consistence resembling that of thick oatmeal. In some places there is added to this the yellowish tinge of bile. The hemorrhage in the right lobe is found to be subcapsular and infiltrates the liver substance. It is essentially a hematoma beneath the capsule. No remnant of normal liver can be made out. Everywhere with slight pressure the liver substance can be removed leaving only the connective tissue framework.

The portal veins at their entrance to the liver are everywhere filled with smooth, firm, yellowish-white clots but slightly streaked with red. (See Fig. 2.) These clots project into all the smaller branches and are definitely adherent to the vessel wall. In most instances they completely

PLATE III.

To Illustrate Drs. Pease and Pearce's Article on "Liver Necrosis and Venous Thrombosis in Horses."

Albany Medical Annals, January, 1907.

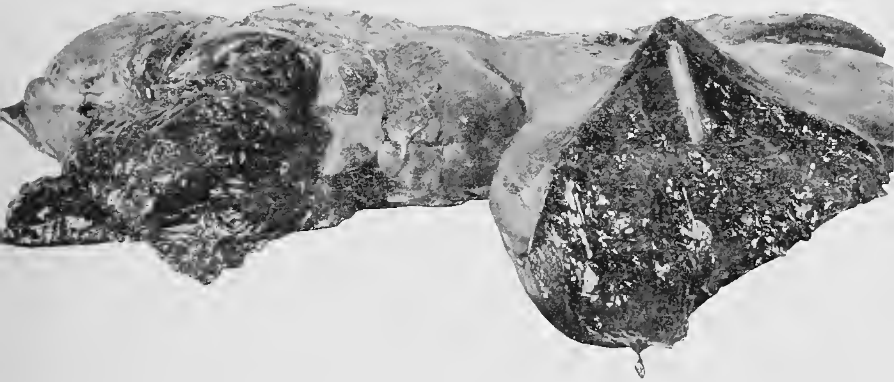

FIG. 1.—Necrosis, Hemorrhage, and Rupture of Liver. Horse 43.

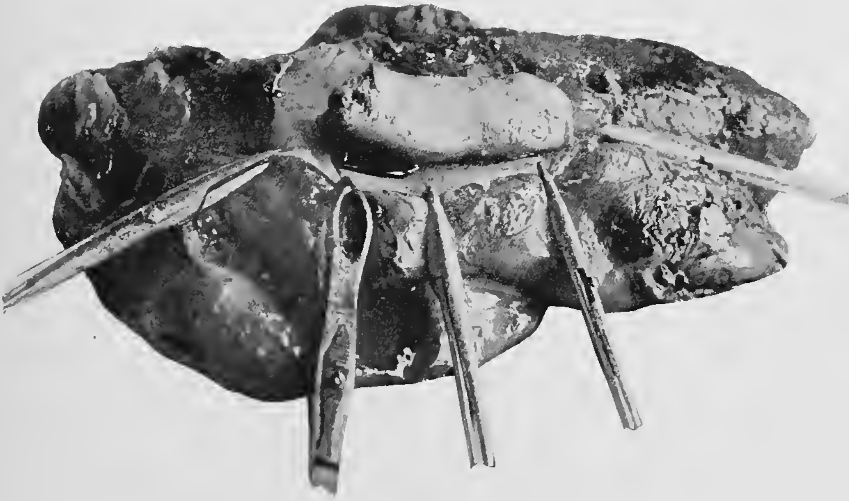

FIG. 2.—Thrombosis of Portal Vein. Horse 21.

occlude the vessels in which they lie. On section through the liver small, firm, yellow, rigid clots protrude from the surface. The hepatic artery is free as are also the aorta and vena cava.

The spleen shows slight thickening of the capsule, and on section are found here and there a few soft swollen areas of a darker red than the surrounding tissue and in the center of each a clot similar to those found in the liver. On dissecting the main branch of the splenic vein an adherent thrombus can be followed for some distance. The splenic artery is free.

There is no accumulation of fluid in either pleural or pericardial cavity. The heart is pale, but otherwise negative. The lungs are pale and neither congested nor edematous. There are no thrombi in the pulmonary, coronary, or other vessels of the thorax. The kidneys are pale and cloudy. The adrenals are swollen and soft.

Careful examination of the vascular system shows no thrombi in vessels other than those of liver and spleen.

Anatomical diagnosis.—Widespread necrosis of liver. Hematoma of the liver. Focal hemorrhages in the spleen. Hemoperitoneum. Thrombosis of the portal and splenic veins.

Histology. Liver.—Sections taken at random from different portions of the liver show practically complete necrosis without leucocytic infiltration. Here and there the nuclei in small portions of a lobule may be distinguished, as may also those of the structures in the larger portal spaces, but otherwise the destruction is complete. Much bile pigment is present in the necrotic cells.

Sections passing through the periphery of the hematoma in the right lobe show this mass to be surrounded by a definite fibrous capsule from which prolongations pass into the adjacent necrotic tissue. In this fibrous tissue is a diffuse deposition of old blood pigment.

Other sections show loose granulation tissue penetrating and replacing the blood clot. Here and there in the older portions are newly formed bile ducts and liver cells, the latter being large, pale, and multinucleated.

Sections through five thrombi differing in size show a uniform structure —a definite network of fibrin enmeshing large numbers of leucocytes. At the periphery the fibrin is compact and hyalin, forming broad bands. Small bands of similar hyalin are found also in the other portions. Only an occasional red corpuscle is seen.

Spleen.—Section through the occluded vein shows a thrombus, similar in structure to those found in the liver and intimately adherent to the vessel wall, which is greatly thinned and infiltrated with lymphoid cells. In the tissues about the vessels a diffuse hemorrhage has occurred. Elsewhere the spleen is normal.

Lymph nodes.—The sinuses are dilated and closely packed with large, pale, endothelial cells. These are but slightly phagocytic. In the lymph nodes are many plasma cells, with, however, no diminution of the lymphoid cells. Throughout the lymphoid tissue is an abundant deposition of old blood pigment.

Adrenal.—Normal.

Lung.—Congestion, moderate edema in focal areas and slight thickening of walls of alveoli.

Kidney.—Cloudy swelling of epithelium of tubules, few foci of lymproid cell infiltration.

Heart muscle.—Cloudy swelling.

Histological diagnosis.—Necrosis of liver with repair about hematoma. Mixed thrombi of portal vessels. Thrombosis of splenic veins with perivascular hemorrhage. Endothelial hyperplasia of lymph nodes with deposition of old blood pigment. Congestion and edema of lung. Cloudy swelling of heart and kidney.

ABSTRACTS FROM CLINICAL HISTORIES AND PROTOCOL.

HORSE 11.—*Clinical notes.*—Horse about 10 years old. Used in the diphtheria service. Had stiff leg joints at time of entering, which gradually became worse until horse was almost constantly confined to its stall.

The maximum antitoxin strength of its serum was approximately 500 units per c.c. During the last six months of its life the horse showed progressive emaciation. After a year and 11 months of treatment the horse suddenly developed the usual symptoms of hepatic rupture, and died in a few minutes.

Autopsy notes.—A superficial examination shows diffuse necrosis and hemorrhage of the liver, with rupture of the capsule and consequent hemoperitoneum.

HORSE 17.—*Clinical notes.*—Sound horse of uncertain age. Diphtheria service. Always remained well and active during period of treatment of two years and one month. Antitoxic strength of serum varied from 200 to 400 units per c.c.

The animal retained its usual weight until death, which occurred suddenly after the development of the usual symptoms of hepatic rupture.

Autopsy notes.—Examination incomplete. Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum.

HORSE 28.—*Clinical notes.*—Sound horse about 12 years old. Diphtheria service. Active during entire period of treatment of two years. Maximum antitoxic strength of serum 400 units per c.c. Gradual loss of flesh during last two months of life. Had frequent abscesses at the sites of injection with accompanying high temperatures. Died during the night.

Autopsy notes.—Examination incomplete. Diffuse necrosis of the liver, with hemorrhage, rupture, and hemoperitoneum.

HORSE 36.—*Clinical notes.*—Sound horse about 10 years of age. Dysentery service. Progressively increasing doses of autolyzed suspensions of surface growth of agar cultures of two strains of *B. dysenteriae* were injected alternately into this horse. They produced very severe reactions, during which the temperature would often rise to 104° F., or over, and the site of the injection would become very much swollen and painful, and the animal would refuse to eat for several days.

After a total of 496 c.c. of these autolyzed suspensions of dysentery bacilli had been administered, living broth cultures of the same strains were administered. They caused much less vigorous systematic reactions.

About seven weeks before death the animal developed a severe diarrhea, which was checked with difficulty. It also began to lose weight, and finally became much emaciated. The animal was found dead early in the morning.

Autopsy notes.—Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum. Other organs, including intestinal mucous membrane, normal microscopically. Cultures from the usual organs were negative. No thrombosis was noted in any of the vessels of the liver, spleen, or lungs, but attention was not directed particularly toward this point.

Histological diagnosis.—Intense diffuse granular degeneration with irregular focal areas of necrosis in the liver.

HORSE 37.—*Clinical notes.*—Sound, active horse of about 12 years of age. Streptococcus service. Received, in gradually increased doses, a total of about three and a half liters of autolyzed salt solution suspensions of a rabbit-virulent streptococcus, grown on the surface of large agar plates, and later about half a liter of broth cultures of the same streptococcus. Small subcutaneous abscesses followed the later injections. The animal retained its weight and activity during the treatment. It was found dead one morning.

Autopsy notes.—Diffuse necrosis of the liver with hemorrhage, rupture, and hemoperitoneum.

HORSE 38.—*Clinical notes.*—Streptococcus service. Age uncertain, but animal appeared to be at least 20 years old. Had somewhat crippled legs. Became emaciated during the last two months of life. The treatment was the same as was given Horse 37 and was started at the same time, except that another streptococcus was used. This animal also died during the night, about two weeks after the death of Horse 37, and the autopsy findings were in general the same as those of that animal.

HORSE 21.—*Clinical notes.*—Sound active mare about 16 years old. Tetanus service. Always well. Remained active and retained its weight during life. She died in the manner already described. (Full protocol will be found in the text.)

HORSE 29.—*Clinical notes.*—Sound active horse about 10 years of age. Tetanus service. Remained well until about two months before death, when it had frequent rises of temperature and difficulty of breathing which were directly due to the toxin injections. During the last half-year had frequent acute abscesses at sites of injection. This horse died in the manner already described.

Autopsy notes, anatomical diagnosis.—Diffuse necrosis of the liver with subcapsular hemorrhages and rupture. Hemoperitoneum. Multiple thrombi of portal veins. Multiple thrombi of pulmonary arteries. Multiple infarcts of the lungs. General lymphatic hyperplasia.

Histological diagnosis.—Necrosis, congestion, and hemorrhage of the liver. Thrombosis of portal veins and pulmonary arteries. Focal edema and congestion of the lungs with slight leucocytic exudate. Acute endothelial hyperplasia of the lymph nodes. Congestion of the spleen. Acute interstitial (non-suppurative) nephritis. Tests of liver and kidneys for amyloid changes were negative.

HORSE 59.—*Clinical notes.*—Diphtheria service. Sound active horse about 10 years old. After eight months of treatment was taken suddenly while in the paddock with difficulty of breathing and evident distress. Respiration became very rapid and labored, and at the same time there was very marked spasmodic tenesmus, but no dung was passed. Pulse rate about 90. The horse became weaker as the above condition continued, and finally was unable to stand, and when down struggled violently, so that it became necessary to kill him about five hours after the onset of the symptoms. The maximum antitoxic strength of the serum was 300 units. The last bleeding occurred about 10 days prior to death.

Autopsy notes, anatomical diagnosis.—Thrombosis of portal veins. Focal hemorrhages of liver and spleen.

Histological diagnosis.—Granular degeneration and focal hemorrhages of liver. Leucocytosis.

HORSE 57.—*Clinical notes.*—Diphtheria service. Sound horse 10 years old. This animal had lived under the same conditions as the other horses in the service for 10 months before the treatment was begun. The toxin injections were pushed with considerable vigor, so that during the four months of treatment he received 14 injections, and had an average of nearly 3.9 days of temperature over 101° F. for each injection given, which is the maximum for any of the horses in this series. The animal appeared to stand them satisfactorily, and gave a serum of 300 units per c.c. at the second bleeding. Immediately after the third withdrawal of eight liters of blood the animal suddenly fell to the floor in a state of collapse. Nothing was thought of this, as it is not an uncommon occurrence when larger amounts of blood are withdrawn. The horse did not attempt to rise later on, and all efforts to stimulate the animal with strychnin, etc., and to support him in slings, were futile. That night and the following day he struggled violently, and could not be quieted with full doses of morphine or chloral. The next night, and also part of the following day, he rested comfortably. Later he again became violent, and as the temperature rose to 106, and as it seemed impossible to control him, he was killed in the evening. His head and shoulders were badly bruised, and as the autopsy was not performed until the next morning, the tissues and organs showed a well-developed gas bacillus infection at that time.

Autopsy notes, anatomical diagnosis.—Acute endarteritis and thrombus formation in the main trunk of the pulmonary artery. Thrombosis of intrapulmonary branch of left pulmonary artery. Atalectasis of portion of left lung. Hemorrhagic infarct of left lung. Cloudy swelling of the myocardium. Fatty transformation of the liver with evidences of gas bacillus infection. No hemorrhage or other evidence of antemortem necrosis was apparent.

Histology.—Complete postmortem decomposition with gas blebs in the liver and lungs. Tests for amyloid changes in all organs were negative.

HORSE 43.—*Clinical notes.*—Diphtheria service. Sound horse about 10 years old. Remained well and active during treatment for two years and two months. During the last few months of life was subject to abscess formation at sites of injection. Its serum showed 500 units per c. c. after three months of treatment, and varied from that point to 700 units during the next year, after which time it varied from 300 to 500 units, until three months before death it dropped suddenly to below 200 units. Death occurred in the manner already described.

Autopsy notes, anatomical diagnosis.—Extensive necrosis of the liver with multiple hemorrhages. (See Fig. 1.) Thrombosis of small branch of the portal vein in the right lobe. Rupture of encapsulated hemorrhages in the peritoneum. Hemoperitoneum. Thrombosis of the splenic veins. Hemorrhage and edema of gastrohepatic lymph nodes. Chronic peritonitis.

Histological diagnosis.—Necrosis and amyloid degeneration of the liver, with moderate regeneration. Chronic hemorrhagic cysts of the liver. Organizing thrombi of portal and splenic veins. Amyloid degeneration of Malpighian bodies of spleen. Proliferation of intima of splenic arteries. Hemorrhage and endothelial hyperplasia of gastrohepatic lymph nodes.

HORSE 50.—*Clinical notes.*—Diphtheria service. Horse of uncertain age, of good condition on entering. Gradually became almost helpless through stiffness of joints and blindness. Had frequent abscess formations at sites of injections. Antitoxic strength of serum never over 300 units c.c., and usually from 200 to 250 units. Was found dead one morning, and stall showed evidences of continued struggling. The front of the stall was covered with frothy mucus. The coughing up of this material has never been observed in the horses dying from rupture of the liver.

Autopsy notes, anatomical diagnosis.—Necrosis and hemorrhage of left lobe of the liver. Congestion of lungs and the right lobe of the liver. General lymphatic hyperplasia. Abscess of subcutaneous tissues of back. Cloudy swelling of heart and kidneys. Acute endarteritis of left renal artery. Thickening of intima of splenic artery. Focal lesions of adrenals. Chronic peritonitis.

Histological diagnosis.—Congestion, edema, hemorrhage, amyloid degeneration, and necrosis of the liver. Chronic interstitial myocarditis. Subpericardial hemorrhage with hyalin degeneration of muscle fibers, and leucocytic infiltration. Edema and congestion of lungs with hemorrhages. Edema and hemorrhages of lymph nodes. Amyloid transformation of Malpighian bodies of the spleen. Localized endarteritis and mesarteritis of left renal artery.

HORSE 56.—*Clinical notes.*—Diphtheria service. Horse about nine years old on entering. Developed stiffness of joints and became badly crippled. Antitoxic strength of its serum was rarely up to 300 units per c.c., and usually showed but 200 units. After a year and five months of treatment the animal was killed.

Autopsy notes.—Macroscopically and microscopically the liver, spleen, kidney, pancreas, adrenals, lymph nodes, lungs, and heart muscle appeared to be normal.

Table I presents a summary of the findings relating to necrosis of the liver and thrombosis in twelve horses which have presented such changes, and also gives those of one horse in whom all the organs were normal, although it had been subjected to active treatment with diphtheria toxin for a period of a year and five months. The other changes found in the tissues of these twelve horses varied to some extent, but such changes did not differ greatly from those to be found in the tissues of fatal cases of diphtheria in man, such as endothelial hyperplasia of lymph nodes, and cloudy swelling of kidney epithelium and heart muscle, etc.

One or two unusual findings were, however, observed. In Horses 43 and 50, belonging to the diphtheria service, amyloid changes were observed in both liver and spleen, and especially in the latter, but were not present in the kidney, heart muscle, or lymph nodes. These animals had developed an unusual number of subcutaneous abscesses at the sites of the toxin injections during the later months of their lives.

In the liver in tetanus horse 21 around the margin of a subcapsular hematoma, and in the necrotic liver of diphtheria horse 43 about the larger portal spaces were found evidences of attempted regeneration in the way of newly formed false bile ducts, and, especially in the latter horse, of columns of newly formed liver cells. In the necrotic livers of the other horses there were no evidences of repair. Also in the tetanus horse 29 there were evidences of beginning interstitial nephritis, of the acute non-suppurative type found in diphtheria of man, accompanying widespread disintegration of the epithelium of convoluted tubules.

A study of Table 1 will show that horses presenting necrosis of the liver did not, in all cases, show thrombosis in any organ, nor in animals presenting both conditions was the thrombosis in the hepatic veins always as extensive in its distribution as the necrosis. On the other hand, two diphtheria horses presented thrombosis without evidences of liver necrosis. Unless, therefore, the thrombosis in some instances is secondary and dependent upon the necrosis, and in other cases upon other conditions, we cannot attach much significance to their fairly close association.

That the necrosis is not usually of sudden or rapid development is shown by the fact that the livers of two horses, tetanus horse 21 and diphtheria horse 43, presented encapsulated hematomas of various sizes scattered throughout the liver substance. The thickness of the capsules and the character of their contents indicated their formation at least several months prior to death, which in turn demonstrated the still earlier existence of extensive necrosis.

With the object of ascertaining whether there existed any common factor in the clinical histories of these horses which might assist in arriving at either the etiology of the liver necrosis or the thrombosis, or of both, the individual factors in the history of each horse which has died since these conditions were noted, have been worked out and are compared in Tables 1, 2, 3 and 4.

It is evident from the fact that some horses in the diphtheria, tetanus, streptococcus, and dysentery services presented diffuse necrosis of the liver, that this condition is not due to any special pathogenic property of any one of the organisms used in the immunizations. If, however, it is the result of the activity of some bacterial property, it is not necessary to suppose that the agent in all cases belongs to either the soluble toxins or the so-called bacterial endotoxins, for the reason that the tetanus horses received only toxin which had been filtered through Pasteur-Chamberlain filters, and consequently no bacterial bodies were injected; and, on the other hand, the streptococcus horses which received large amounts of dead cultures were equally affected.

It hardly seems probable that any of the constituents of the various media used in the preparation of the toxins and toxic products, such as the meat extractives, peptone, etc., could be the causative agent of the liver necrosis, for the reason that the two horses of the streptococcus service (37 and 38) received only about 500 c.c. of broth containing such materials during a period of about one and three-quarters years, the other later injections consisting of suspensions of bacteria or their bodies in physiological salt solution. (See Table 2.)

Neither can any effect produced by the repeated abstraction of blood from such horses be the main cause of the liver necrosis, for, as is seen in Table 2, Horse 36 in the dysentery service was bled only one liter on a single occasion, and the streptococcus horses 37 and 38 had bled eight liters, abstracted on only six and seven occasions respectively during a period of a year and three-quarters. On the other hand, Horse 56 of the diphtheria service was bled eight liters on 18 occasions during a period of a year and a half, and at death its liver was absolutely normal.

It is likewise possible to exclude the antiseptics used in the preservation of the bacterial toxic agents as an important factor in the production of liver necrosis, although nearly all the toxic materials administered contained from 0.3 to 0.5 per cent of either carbolic acid or trikresol. A study of Table 2 will show that the actual amounts of these antiseptics received by the different horses varied from about 2.5 c.c. during 11 months in the case of dysentery horse 36, and about 17 and 19 c.c. in the streptococcus horses 37 and 38 respectively, to 165 and 235 c.c. in the tetanus horses 21 and 29 respectively, and from 190 to 385 c.c. in the various diphtheria horses presenting necrosis of the liver. In other words, the horses receiving the larger amounts of antiseptics lived the longer periods.

Nor could we explain the necrosis of the liver by any general disturbance of metabolism due to the injections of the bacterial toxic agents, for some of the animals which showed the most diffuse necrosis were to all outward appearances and according to their weight in excellent physical condition, as is indicated in Table 2.

TABLE 2.

SHOWING RELATION OF THE MATERIALS INJECTED AND OF REPEATED BLEEDINGS TO LIVER NECROSIS.

HORSE.	Toxic Broth Injected.	Autolyzed or Dead Bacterial Suspensions.	Amount Carbolic Acid Injected.	Number of Bleedings (8 Liters Each).	Condition at Death.	Extent of Necrosis.
11.............	42 liters		210±c.c.	21	Poor	Extensive.
17.............	59 "		295±	25	Good	"
28.............	38 "		190±	20	Poor	"
36.............		800 c. c.	2½±	0	"	"
37.............		4 liters	17±	6	Good	"
38.............		4½ "	19±	7	Poor	"
21.............	63 liters		165±	29	Good	"
29.............	78 "		235±	35	"	"
43.............	77 "		385±	25	"	"
50.............	50 "		250±	18	Poor	Left lobe.
56.............	33 "		165±	18	"	No necrosis

There is also no apparent reason for believing that the conditions under which such horses are kept in antitoxin stables is the main factor in the causation of the necrosis. Diphtheria horse 56 was kept under the same conditions as the others for a period of a year and a half, and at autopsy the liver was normal.

A careful study of the temperature charts and a knowledge of the manner in which the horses withstood the injections will, perhaps, give as likely an explanation of the causation of the necrosis as can be found. In Table 3 will be found the number of days during the treatment of each horse, in which the temperature stood at the various points from 101° to 105°+ Fahrenheit. It will be seen that a fair degree of uniformity exists in this number of days of fever in the animals which had necrosis of the liver. These increases of temperature cannot be accepted, however, as an exact index of the character of the reaction, as some horses commonly have considerable fever without any other manifestation of serious disturbance after toxin injections. However, the variations in the temperature curves are due largely to the type of immunization. Thus the dysentery horse had apparently fewer days of temperature than those used in the diphtheria work, but he lived under the treatment only about one-half as long as the latter. It is well known that horses are particularly susceptible to injections of cultures of true or paradysentery bacilli; and this horse withstood the injections very poorly. On the other hand, the horses treated with injections of even large doses of tetanus toxin show only slight disturbances, and in harmony with this is the long duration of the period of treatment in horses 21 and 29, each of which lived considerably over three years. The two streptococcus horses withstood the injections about as well as the diphtheria animals. Each lived approximately a year and three-quarters, and that was nearly the average life, a year and eleven months, of the five diphtheria horses.

TABLE 3.

SHOWING RELATION OF REACTIONS DUE TO TOXINS INJECTED TO LIVER NECROSIS.

HORSE.	Disease.	Duration of Treatment.		Number Injections.	Days of Temp. Over 101° Fahr.					Average Days of Temperature for each Injection.
					101 to 102	102 to 103	103 to 104	104 to 105	Total.	
		Yrs.	Mos.							
11.........	Diphtheria	1	11	75	95	73	14	1	183	2.4
17.........	"	2	1	77	85	75	22	2	184	2.4
28.........	"	2		69	92	74	38	9	213	3.1
36.........	Dysentery		11	46	86	62	14	4	166	3.6
37.........	Streptococcus	1	9	54	76	44	19	2	141	2.6
38.........	"	1	9½	60	98	48	5	1	152	2.5
21.........	Tetanus	3	3	126	95	69	9	1	174	1.4
29.........	"	3	7	138	135	53	8	2	198	1.4
43.........	Diphtheria	2	2	77	92	65	31	3	191	2.2
50.........	"	1	7	64	79	39	20	0	138	2.1
56*........	"	1	5	59	63	57	34	2	146	2.4

As the horses used in each service lived approximately the same length of time under their respective treatments, and as the animals receiving the injections of the toxins causing the milder reactions lived for considerably longer periods than did those receiving toxins producing the most violent reactions, and as we have excluded other possible factors, we are led to the conclusion that the liver necrosis is, without much doubt, mainly the effect of the administration of repeated doses of the bacterial products.

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*No liver necrosis in this horse.

That some of the other factors which appear to be excluded by our findings may be contributory to the main causative agent in some instances cannot be denied.

A possible relationship between the effect of the toxic products of these bacteria on the liver cells and the production of antitoxic or other anti-bodies is not capable of either positive or negative determination from the available data.

In the diphtheria and tetanus horses under consideration no relationship can be made out between the course of the necrotic changes in the liver and the well-known progressive decrease in the antitoxic strength of the sera of some horses after prolonged treatment. Thus diphtheria horse 50, which had necrosis of the liver, gave an antitoxin of from 300 to 350 units per cubic centimeter in only two early bleedings out of a total of 15, the others producing sera of from 200 to 250 units. On the other hand Horse 56, which showed a normal liver when killed after an immunization life of one year and five months, gave almost identically the same grades of serum in seventeen bleedings. That is, the early bleedings gave sera of 400 units, and those subsequently from 300 down to 200 units, which was the strength at the time the animal was killed. These findings would seem to indicate that the customary decrease in antitoxic power, which occurs in the sera of many horses as their immunization proceeds after the first few months, is not exclusively due to a progressive liver necrosis. However, the amount of data obtained does not permit us to draw any conclusions concerning the possible relation of the liver to antitoxin production. The bleedings are too infrequent, and the continuation of the antitoxic power of the serum is probably dependent upon so many factors that the absence of liver necrosis in one horse whose serum had shown the usual progressive loss of power, is entirely insufficient evidence to warrant the exclusion of the liver as a factor in antitoxin production.

Brunton and Bokenham[1] have endeavored to show that the liver is capable of producing diphtheria antitoxin by the action of toxin passed through the portal venous system. While it might be questioned whether they have clearly proven the formation of true antitoxin, they undoubtedly showed that the liver cells have an affinity for pure diphtheria toxin, and are capable of at least greatly reducing the poisonous power of the crude product.

A similar affinity of the liver cells of some invertebrates for tetanus toxin has been claimed by Metchnikoff.[2] He states that in scorpions injected with tetanus toxin the liver is the only organ which absorbs and retains the toxin.

If the liver is capable of absorbing large amounts of the toxic bacterial products, and if their direct action on it is the means of producing liver necrosis, then in most horses treated with such agents the liver is very probably capable of disposing of large amounts of these products without injury; for the liver necrosis is not present in many horses, at least, which have come to autopsy after injections of considerable amounts of diphtheria toxin distributed over several months. (See history of Horse 56.)

In view of recent work on autolysis of liver tissues *in vitro,* it may not be out of place to consider the possibility that this late necrosis is due to alterations or disturbances of those factors which prevent the action of the autolytic ferments normally present in the liver.

Baer and Loeb[3] have shown that weak alkalis retard and weak acids stimulate the autolytic ferments in the liver, and that the elements in normal serum which strongly retard or prevent autolysis are the serum albumin and the fibrinogen, while the serum globulin has the opposite effect, namely, a strong stimulating action on the autolytic ferment.

Hiss and Atkinson,[4] Butjagin,[5] and others claim that an increase in the globulin content of the blood occurs during active immunization, although this is disputed by Müller.[6]

Butjagin also demonstrated a gradual decline in the alkalinity of the blood during the later part of the period of immunization.

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[1] *Jour. Path. and Bact.*, 1904, x, 50.
[2] *L'Immunité*, etc., Paris, 1901, p. 343.
[3] *Arch. f. exper. Path. u. Phar.*, 1905, liii, 1.
[4] *Jour. Exper. Med.*, 1900, v, 47.
[5] *Hyg. Rund.*, 1902, xii, 1193.
[6] *Beiträge z. chem. Physiol. u. Path.*, 1905, vi, 454.

In view of the work of Baer and Loeb, the occurrence of these or other similar blood changes may have some relations to the development of the liver necrosis or autolysis.

THROMBOSIS.

Of the horses upon which careful autopsies were performed and which presented necroses of the liver, extensive coexisting thrombosis of the veins of that organ was found in one (Horse 21), and to a lesser extent in two others (29 and 43). In the horses treated with streptococcal and dysenteric bacterial products, no careful searches of the entire substance of their livers with this point in view were made.

In one diphtheria (43) and in one tetanus (21) horse the veins of the spleen were likewise the seat of thrombosis to a greater or less extent. The other tetanus horse (29) had extensive thrombosis of the pulmonary arteries and infarction of the lungs.

As has been stated, two diphtheria horses had thrombosis occurring without necrotic changes in the liver. In one (59) the thrombosis was confined to three large branches of the portal vein in the liver, while in the other (57) the thrombosis was present in the main branch of the pulmonary artery and in the intrapulmonary branch of the left pulmonary artery. In the latter horse the clinical manifestations arose immediately after a withdrawal of the usual eight liters of blood, and may have been due to the formation of a blood clot at the site of this operation and the detachment and passage of the clot into the venous circulation. The thrombus in the main pulmonary artery was in the form of a pedunculated vegetation about the size of a walnut. The horse apparently suffered considerable thoracic pain, and was so weak as to be unable to stand even with the assistance of slings.

The other horse (59) with localized thrombosis of the portal veins gave indications of great pain in the abdominal cavity, with tenesmus, and also complete prostration and excessively rapid respiration and a high pulse rate. After the continuation of these symptoms for about five hours the animal was killed, and the autopsy performed immediately.

If the conditions operating to produce the thrombosis in this case are the same as in those where the thrombosis coexisted with liver necrosis, it is remarkable that it should have occurred as early as the eighth month of the immunization period, and that the clinical symptoms should be so much more severe than in those cases where thrombosis occurred later and more extensively.

In looking for some factor or condition operative during the period of treatment which might be considered as of etiological significance for the thrombosis, we are not afforded as much data as we would like, owing to the failure to examine and note particularly the presence or absence of thrombi in the first few animals which died from rupture of the liver with hemorrhage. Thus we have no definite information on this point in three diphtheria, one dysentery, and two streptococcus horses.

From the data tabulated in Table 4 it can be seen that by excluding the horses with early thrombosis the treatment given and its effects on the three remaining horses are quite similar. The only exception is to be found in a considerable difference in the amounts of carbolic acid or trikresol which the horses received with the toxins injected. We are of the opinion that these antiseptics played no essential part in the production of the conditions favoring thrombosis.

TABLE 4.

Relation of the Treatment of Horses to the Development of Thrombosis.

Number.	Diseases.	Immunization Period.	Liters of Broth Injected.	Amount of Carbolic Acid Injected.	Days of Tem. over 101°	Number Bleedings of 8 Liters Each.
59.........	Diphtheria	8 mos.	16½	82± c.c.	91	7
57.........	"	4 "	5½	27±	54	43
21.........	Tetanus	3 yrs. 3 "	63	165±	174	29
29.........	"	3 " 7 "	78	235±	198	53
43.........	Diphtheria	2 " 2 "	77	385±	191	25

We cannot, however, readily exclude in this way a possible influence favoring thrombosis by the injection of those elements which make up the broth used for toxin production, such as peptone, meat extractives, etc. Likewise we cannot exclude the effects of the repeated abstraction of eight liters of blood every three or four weeks. We are unable, therefore, by any process of exclusion to form any definite opinion of the part played in the thrombosis by the pathogenic activity of the bacterial toxins injected into these horses.

If, however, we ascribe to the early thromboses the same etiological conditions as bring about the late thromboses, then we can find no common factor in the treatment of our horses which might have been operative in the determination of this condition.

There are, however, some noteworthy features in the relation of thrombosis to the liver necrosis in some of the horses.

Thus in Horse 50, which was the only animal with necrosis of the liver which was thoroughly examined for thrombi and none found, the necrosis and hemorrhage of the liver was not general but localized almost exclusively in the left lobe, and was evidently not so far advanced as in the other animals. As the autopsy also revealed myocarditis with small subpericardial hemorrhages, and amyloid degeneration of the liver and spleen, local endarteritis, edema, and congestion of the lungs with small hemorrhages, it is not unlikely that the animal did not die from the effects of the liver necrosis, especially as there was no rupture of that organ. It is not improbable, therefore, that thrombosis would also have occurred in this horse if he had lived longer.

In Horse 29 the portal veins in which thrombi were found corresponded closely with the areas of necrosis in the liver, and it was noted that the thrombosis seemed to proceed from the smaller veins outward into the larger branches, ending there in large, round-ended clots.

In Horse 43 the extensively necrotic liver showed thrombosis only in one small portion of the right lobe, but considerable thrombosis occurred in the spleen.

Thus, taking the findings as a whole, it can be stated that while all necrotic areas in the liver did not have coexisting thrombosis, there were no thrombi in the portal veins other than in the necrotic portions, except in the two horses already described which died with early thrombosis without necrosis. It is possible, therefore, that in some animals, at least, the portal thrombosis may be caused by lesions of the vessel walls secondary to the liver necrosis.

It is the opinion of Smith[1] that the pathological effects of the periodic losses of blood in antitoxin horses lead in certain cases to serious derangements and death. He shows that in many horses which have been bled five liters every three or four weeks for periods of from nine months to over four years, the red blood corpuscles have a reduced osmotic tension. He believes that this condition is due to the repeated bleedings and not to the toxin injections.

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[1] *Jour. Med. Res.* 1904, xii, 385.

In Pettit and Girard's case of necrosis of the spleen in an antiplague horse, the authors express the qualified opinion that the necrosis was not due to the periodic bleedings.

In so far as necrosis of the liver is concerned, our data do not warrant the conclusion that the periodic bleedings have any special etiological relation to it. If, therefore, the lowered osmotic tension is due to the repeated losses of blood, it is not probable that such lowered tension is in any way responsible for the liver necrosis. Whether it is or is not a factor in the causation of the thrombosis we are not prepared to state.

Butjagin has shown the presence of this phenomenon and also the existence of such alterations in the blood serum as an increase in the specific gravity, changes in albumin and globulin content, electrical conductivity, alkalinity, and refractive index during the immunizing process.

Similar work on one or more of these aspects of the subject has been reported by Müller[1] and others.

What relation exists between these alterations in the morphological, chemical, and physical conditions of the blood constituents and the pathological conditions noted by us, remains to be solved.

SUMMARY.

In a series of twelve horses, actively immunized with the products of certain pathogenic microorganisms, autopsies revealed widespread liver necrosis in nine, and localized liver necrosis in one.

Thrombosis of the portal veins was present in three, of the splenic vein in two, and of branches of the pulmonary artery in one, of the nine horses showing widespread necrosis. One horse had thrombosis of branches of the portal veins and another of the pulmonary artery without liver necrosis. Six horses were not carefully examined for thrombosis.

The evidence obtained tends to exclude the materials such as peptone, beef extractives, and antiseptics, such as carbolic acid, injected with the toxins, and also the repeated bleedings practiced, from any important rôle in the production of the liver necrosis. On the other hand, the evidence leads to the conclusion that the toxic bacterial products injected are directly or indirectly responsible for the production of this pathological condition.

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[1] *Loc. cit.*

The evidence is not sufficient to determine which, if any, of these factors is responsible for the occurrence of the venous thrombosis. A possible etiological action by the antiseptics injected is excluded. In some cases the portal thrombosis may result from the liver necrosis.

NOTE.—Since this paper went to press another horse (No. 60) has died after a year and four months of treatment. During the first four months of this period it received diphtheria toxin, and after that until death small doses of tetanus toxin. The horse had a very slightly varying temperature of from 104° to 106° during the two weeks prior to death, and gradually became weaker during the last few days of life, and died during the night. Just prior to the onset of the high temperature an edematous condition of the genital sheath developed, followed by a tremendous increase in the size of the penis, apparently due to venous stasis. Later the use of the left hind leg became impaired.

At autopsy thrombosis of the left iliac vein, the inferior vena cava, the veins of the tissues about the penis, the splenic vein outside the spleen, the portal vein, and some of its branches in the liver, and of some of the pulmonary arteries was found. There was no evidence of necrosis in the liver. There was a general hyperplasia of the lymph nodes.

AFFECTIONS OF THE THYROID GLAND:

A CLINICAL AND PATHOLOGICAL STUDY.*

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PLATES IV, V, AND VI.

During the past few years as a result of the great advances in surgery of the thyroid gland, the study of the many diseases of this organ has been placed upon an intelligent clinical and pathologic basis. There still remains, however, a lack of uniformity not only in the classification of the various lesions but also in the interpretation of their etiology and their pathologic significance. It was with the object of adding, if possible, to our orderly knowledge of the pathology of the thyroid that this study of a large series of cases was undertaken.

Material.—Since the opening of the Bender Laboratory, in 1896, a period of about ten years, material removed at operation from sixty-one cases of thyroid disease has been examined. It

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is upon this material, mainly from the surgical clinic of the Albany Hospital, together with three of my own cases, that this present study is based. Including, as it does, examples of all of the more important affections of the thyroid gland, with careful gross and microscopic descriptions, this group of cases offers unusual opportunities for investigation.

This material may be classified as follows:[1]

Class.	Disease.	No. of Case.
I.	Simple hypertrophy	26
II.	Adenoma	9
III.	Recurrent adenoma	3
IV.	Cyst	12
V.	Metastatic thyroid tumor	1
VI.	Exophthalmic hypertrophy	6
VII.	Chronic thyroiditis	1
VIII.	Tuberculosis	2
IX.	Carcinoma	1

These lesions fall naturally into three groups,—the hypertrophies, the tumors, and the inflammations,—and should perhaps more properly be discussed in this order. Several departures, however, will be made in order to more clearly present the relations of the various lesions. Simple hypertrophy and adenoma as they possess, histologically, much in common, will be considered in sequence, thus affording a better opportunity for differentiation. The exophthalmic type, aside from the fact that it represents a diffuse process, bears no points of resemblance either clinically or pathologically to the simple colloid form and will therefore be considered by itself. The cysts have been found to have such close relationship to the adenomata that they may be considered with the latter.

In the study of each type of lesion, a systematic manner of presentation will be pursued as far as possible. First, a tabulated list of the cases, giving the age of the patient at the time of operation, the age of onset, the duration of the disease and the ultimate outcome when possible, will be presented. Following this one or more typical cases will be related in detail, with a brief clinical note and a complete pathologic study. When other cases offer points of interest or importance, not already covered in the quoted cases, attention will be directed to these special features in the general discussion. The etiologic and pathologic significance of the group as a whole will then be considered, and finally, after the consideration of each separate group, a résumé will be made of the main points in diagnosis and treatment of thyroid lesions in general.

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[1] To these might be added, to make a classification complete, the sarcomata, the fibromata and the mixed tumors, together with acute thyroiditis, all of which are very rare affections and have not occurred in this series.

I wish here to express my thanks to Dr. Pearce for the privilege of using the material at the Bender Laboratory, and also indirectly to Dr. Blumer, whose careful records has made this study possible. Also I wish to thank the surgeons of the Albany Hospital, especially Drs. Vander Veer, Macdonald and Elting, who have allowed me access to their clinical records.

I—SIMPLE HYPERTROPHY (COLLOID HYPERTROPHY). TWENTY-SIX CASES.

No.	Age of onset.	Age at operation.	Duration.
1	22	23	16 months.
2	24	25	12 months.
3	......	68	....
4	13	13	6 months.
5	......	....	....
6	......	....	....
7	......	30	....
8	24	25	12 months.
9	......	43	....
10	......	42	several years.
11	42	43	1½ years.
12	40	43	3 years.
13	16	18	2 years.
14	24	27	3½ years.
15	13	23	10 years.
16	13	15	2 years.
17	32	40	8½ years.
18	44	62	18 years.
19	11	18	7 years.
20	......	....	....
21	15	49	34 years.
22	......	47	....
23	36	53	17 years.
24	......	....	....
25	......	56	....
26	......	28	....

Average at onset, 24 years; average age at operation, 36 years; average duration, 7 years, 4 months; females, 21; males, 3; sex not stated, 2.

Case I.—(Path. No. 05-1011.) Male, aged 18; for 7 years has had enlargement of the neck with at times dyspnœa and some prominence of the eyes noticed. His mother is said to have had the same condition.

Physical Examination.—A symmetrical enlargement of the entire neck anteriorly and laterally, but slightly greater on the right side, is seen. The enlargement extends outward and backward on either side and is felt deep under the sterno-cleidomastoid muscle.

Operation, June 15, 1905, by Dr. G. E. Beilby. Cocaine. Transverse Kocher incision. The thyroid gland, with the exception of a portion of the upper part of the left lobe about 4x4 cm. in extent, was removed without difficulty. The right lobe is larger than the left and extends more deeply into the tissues.

Patient made an excellent recovery. In January, 1906, the patient's health was excellent.

Pathology.—Macroscopic Examination: Specimen consists of a thyroid gland showing distinctly right, left and median lobes. Weight, 530 grammes. Left and median lobes have been removed entire; a portion of right lobe is absent. The left lobe measures 12.5x5x4 cm., the median 4x2 cm. and the right 10x5x6 cm. The mass is definitely encapsulated, of firm consistence, distinctly lobulated and of a dark red color. The blood-vessels of the capsule are very large and tortuous. The right and left lobes are somewhat symmetrical and more or less kidney-shaped, with flattening of the posterior surfaces. The right lobe is of somewhat greater diameter anterio-posteriorly than the left. On section right lobe is seen to be grayish yellow in color and from the cut surface escapes a thick gelatinous material. It is lobulated; the lobules being composed of numerous alveolar spaces the walls of which are formed of rather firm bands of connective tissue and in which is a colloid material of a clear translucent appearance. Very many large blood-vessels are seen on section. No cysts are present. The left lobe is similar in all respects to the right.

Microscopic Examination.—Sections from four different portions of mass all show practically the same condition. In general the structure is that of the normal thyroid gland. The gland acini, however, are greatly dilated and filled with a homogeneous colloid material which stains with eosin. These acini for the most part are lined with a single layer of cuboidal epithelium. In many are blood-corpuscles and cholesterin crystals. The capsule of the gland is very delicate, and there is but a moderate amount of connective tissue throughout the gland substance.

Microscopic Diagnosis.—Simple colloid hypertrophy.

Case II.—(Path. No. 97-5). Female, aged 23, single. History of enlargement of the neck in the region of the thyroid for 13 years. The enlargement has gradually increased. Recently patient has complained of dyspnœa, dysphagia and nervousness. No exophthalmus.

Operation.—November 15, 1897, by Dr. Macdonald.

Pathology.—Macroscopic Examination: Specimen consists of a lobulated mass of tissue of firm consistence, measuring 12x6x4 cm. It is divisible into two lateral lobes and a central portion, which probably represents the original thyroid gland. The surface is smooth for the most part, but in places, particularly posteriorly, is covered by vascular adhesions. The cut surface has a yellowish gray color, is irregularly divided into lobules, and is dotted here and there with cysts, containing a yellow, jelly-like material. This surface is smooth and glistening and covered with a translucent, sticky material. There are no signs of old or recent hæmorrhage into the gland substance.

Microscopic Examination.—The tumor consists of tissue having in a general way the appearance of thyroid gland. It differs from this structure only in a marked increase in the size of many of the gland acini which contains a large amount of colloid material. *Microscopic Diagnosis.*—Simply colloid hypertrophy.

Case III.—(Path. No. 05-996). Male, aged 60. History of goitre for 18 years which, though of large size, caused no symptoms until two months ago, when severe dyspnœa and dysphagia developed.

Operation.—September 26, 1905, by Dr. Elting.

Pathology.—Macroscopic Examinations: Specimen consists of a flattened encapsulated dark red mass of tissue measuring 11x8x5 cm. having the general appearance of an enlarged thyroid gland. One surface is regular in form and is covered by fine adhesions; the other surface shows irregular lobulations separated one from another by deep fissures. The capsule contains a rich plexus of veins. Loosely attached to this mass is another similarly encapsulated mass 6x3.5x2.5 cm. which is pinkish red in color, lobulated and the seat of numerous small cysts. The surface is covered with fine adhesions. The cut surface of the larger mass shows a greatly thickened capsule surrounding well-marked lobules which have a smooth, glary surface, and appear to be filled with colloid material. The smaller mass on section shows a similar capsule, paler in color and with smaller, less well-marked lobules, and numerous small cysts filled with yellow blood-stained fluid.

Microscopic Examination.—Sections show structure of thyroid gland with capsule greatly thickened. The acini are greatly increased in size and number and filled with colloid. There is no increase in the interstitial substance or in the cells lining the acini.

Microscopic Diagnosis.—Simple colloid hypertrophy.

These three cases illustrate very well this type of enlargement. It is characterized clinically by symmetrical increase in size, which is usually not rapid but extends often over many years. It is true that one lobe may be larger than the other, but the essential change is a diffuse involvement, and the term "simple goitre" or "simple hypertrophy" should be applied only to those lesions which thus involve the entire gland.

Histologically, the characteristic feature is a dilatation of the thyroid vesicles, the result of the increased colloid secretion. There is lack of uniformity in the size of the vesicles, but it is rare to observe any portion of the gland which shows normal vesicles. The connective-tissue stroma in the earlier cases is often found to be somewhat scant, but definite lobulations can always be made out. After the condition has existed for a number of years secondary changes may produce a rather complex picture. These are most frequently hæmorrhage into the alveoli, with associated degeneration and pigmentation in focal areas. Infiltration of leucocytes and lymphoid and plasma-cells is not infrequent. The connective tissue in cases of long standing is usually very abundant. Calcification is common as a late degenerate change. Cysts of large size in a gland showing simple hypertrophy have not been observed. Minute smooth walled cysts formed evidently by the rupture of the walls of adjacent vesicles, with fusion of their colloid contents, are commonly present.

Etiology.—It will be remembered that in the early embryonic thyroid colloid is not present in the epithelial vesicles. The colloid secretion makes its appearance at about the time of birth and first in small amounts, but with the advancing age of the child the individual vesicles show increased dilatation; the gland probably attaining its most active secretory stage during youth or early adult life. An enlargement of the thyroid at this period is very common, but it usually disappears at twenty-three to thirty years of age. This enlargement probably represents a simple hypertrophy of the organ. In explaining this condition of simple hypertrophy, then, it seems proper to infer that in a certain number of cases, instead of a subsidence of this physiologic hypertrophy, the process in an exaggerated form continues and a permanent hypertrophy is the result. In this series it is seen that while before twenty years of age only four cases came to operation, in six the age of onset was before twenty and in four others, in which the age of onset is stated, it was between twenty and thirty years, making nearly one-half of the recorded cases appearing either in youth or early adult life. Pregnancy in a few instances has apparently been the exciting cause.

In simple hypertrophy there is as a rule no symptoms except those produced by pressure upon the structures of the neck. Circulatory disturbances with extreme enlargement seem to be fairly common. Vertigo, which is frequently a symptom, is due, possibly, to pressure of the enlarged gland upon the blood-vessels of the neck. The duration of the condition varies greatly, for the patient seldom seeks advice until the pressure symptoms become severe. Mere deformity causes no concern, but when respiration or deglutition becomes difficult relief is sought. The periods of time represented in these cases vary from a few months to thirty-four years. The size to which the gland may attain also varies greatly. There seems to be no relation between the duration of the condition and the size of the gland. The case showing the most extensive hypertrophy in this series is Case I, quoted above.

In the condition of simple hypertrophy, then, three things may occur. First, there may be a subsidence of the active secretory process after puberty or during young adult life, and a diminution of the amount of colloid present with a return of the gland to its normal size. These are the cases of moderate enlargement. Second, the epithelium may cease to secrete colloid material after a certain age is reached, but fail to undergo retrogressive changes and the enlargement become a permanent one. Instances of this nature are frequent. The hypertrophy is of moderate degree causing as a rule no subjective symptoms, and but rarely demanding operation. Third, a condition similar to No. 2, in which in addition we see in later life, after a quiescence of many years, a rapid increase in the size of the already hypertrophied organ. This enlargement is apparently due to two causes —an increase in the colloid secretion, as observed in the primary enlargement, and an actual reproduction (hyperplasia) of thyroid tissue. This latter is apparently the process present in the majority of cases. Only a portion of the gland may be secondarily affected. The following case, which clinically was considered to be malignant, illustrates this type.[1]

Case IV.—(Path. No. 05-1114). Female, aged 53, goitre with slow growth for 17 years. First began during pregnancy. During the past seven months the enlargement has been rapid and confined chiefly to the left lobe. Dyspnœa and dysphagia marked.

Operation, October 25, 1905, by Dr. Vander Veer. Considerable difficulty was experienced in removing the gland, owing to its deep attachments.

Pathology.—Macroscopic Examination: Usual appearance of old hypertrophic gland with increase of connective tissue, degeneration and calcification in areas, but in addition a large amount of comparatively normal thyroid tissue, differing perhaps in that it has a more cellular appearance.

Microscopic Examination.—The sections show in general a simple hypertrophy with fairly large colloid vesicles lined by the usual epithelium. Here and there, however, are areas of small vesicles, some filled with cells and others containing a little colloid representing young thyroid tissue in various degrees of development. Small masses of epithelial cells are not infrequently observed outside of the colloid vesicle and probably represent focal zones of new thyroid tissue or compressed epithelial vesicles.

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[1] Under "Carcinoma" will be discussed the frequency with which hypertrophied glands of this nature undergo carcinomatous changes.

The histologic appearance in this case suggested the possibility of carcinoma. There is, however, no definite evidence of invasion of the old connective-tissue stroma by the new-formed thyroid tissue. This is a histologic picture frequently observed in cases of old simple hypertrophy in which there has occurred recent growth. Patient made a good recovery from the operation and was well six weeks later.

II.—ADENOMA; 9 CASES

No.	Age of Onset.	Age at operation.	Duration.
1		38	
2	16	21	5 years.
3	37	55	18 years.
4		24	
5	18	23	5 years.
6	25	26	1 year.
7	35	40	5 years.
8	28	30	2 years.
9		43	

Average age at onset, 26 years; average age at operation, 33 years; average duration, 7 years; female, 8; male, 1.

Case V.—(Path. No. 755). Male, aged 55. Onset of tumor 18 years ago in region of thyroid. Has grown larger during the last two years. No symptoms except tumor.

Operation, September 26, 1904, by Dr. Elting. Excision of tumor of left lobe. The right lobe and isthmus seemed normal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor of the thyroid, measuring 8x6x3 cm. Tumor mass has been cut open. On section it presents a rough nodular surface mottled with dark red areas. Surrounding these is a brownish yellow zone and still further out a deep red finely granular zone. The lighter areas are approximately 1x.5 cm., the dark red areas measuring about 2x1 cm.

Miscroscopic Examination.—There is distinct hyperplasia of both glandular and interstitial tissue, the glandular elements in places being massed together and compressed, with irregular outlines; in other places dilated and filled with colloid material; in still other areas the glandular elements are atrophied with marked increase of interstitial tissue, which is highly œdematous and hyaline.

Microscopic Diagnosis.—Mixed adenoma of the thyroid gland.

Case VI.—(Path. No. 05-1207). Female, aged 23. Tumor for 5 years. Rapid enlargement during the past eight months; dyspnœa. Tumor of the right lobe pushing the trachea and larnyx to the left.

Operation, November 14, 1905, by Dr. Elting.

Pathology.—Macroscopic Examination: Specimen consists of a definitely encapsulated tumor 10x5x8x6 cm. Capsule is smooth and apparently free from adhesions. At one pole is a small irregular tumor. The capsule is very dense and fibrous. On section the tumor presents a uniform grayish appearance. Tissue is exceedingly soft and friable. No fibrous bands are seen. In the centre of the mass the tissue is disintegrated and there is found a small cavity filled with blood-stained colloid material. On section, the smaller tumor attached to one pole of the larger has the appearance of normal thyroid tissue and evidently represents the isthmus of the thyroid gland.

Microscopic Examination.—(See Fig. 1.) The general structure of thyroid tissue can be seen, but there are no definite lobulations as are found in the normal and hypertrophied gland. The thyroid vesicles, however, are greatly enlarged and filled with a homogeneous colloid material which stains with eosin. In some areas epithelium lining the individual vesicles has disappeared and their contained colloid has coalesced, forming large irregular pink staining masses. Throughout the colloid material is seen isolated cells and clumps of cells which stain poorly and which represent the desquamated epithelium. There are also numerous red-blood cells. When an epithelial lining is present instead of a single layer of cells we see often several layers, and here the cells stain very poorly and have no definite arrangement. The connective-tissue stroma is very scant and the alveolar walls are delicate. There are a few small epithelial vesicles which contain no colloid and represent young thyroid tissue. The general picture is one of early degeneration.

Microscopic Diagnosis.—Colloid adenoma of the thyroid.

CASE VII.—(Path. No. 64-5.) Female, aged 26. Duration of illness 8 months. The prominent symptoms are pain, dyspnœa and dysphagia.

Operation, February 20, 1899, by Dr. Vander Veer. No note on operation.

Pathology.—Macroscopic Examination: Specimen consists of a globular nodule measuring 4x3x1.5 cm. It is completely encapsulated. Its outer surface is covered here and there with torn adhesions which are attached to the capsule. The nodule is soft in consistence. On section the cut surface bulges somewhat; it is mostly of a gray-white color and rather translucent in appearance. Scattered through it are a few whiter areas suggestive of necrosis and one or two minute hæmorrhagic points.

Microscopic Examination.—The section shows both the capsule and tumor substance. The capsule is composed of several layers of fibrous tissue, in the outermost layer of which can be seen compressed thyroid vesicles probably the result of the encroachment of the growth upon the normal gland-tissue. The tumor proper is made up of closely packed epithelial vesicles, which as a rule are empty or have only a cellular content. In this respect the tissue resembles that of the fœtal thyroid, but differs in that the cells are of a higher type. In some of the vesicles, farthest from the periphery, there is a small amount of colloid present, this probably representing the oldest portion of the growth. The connective-tissue stroma is very scant and there are no lobulations visible.

Microscopic Diagnosis.—Mixed adenoma of the thyroid gland.

CASE VIII.—(Path. No. 05-95.) Female, aged 21 years, married. A tumor the size of a marble appeared in the region of the right lobe of

PLATE IV.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

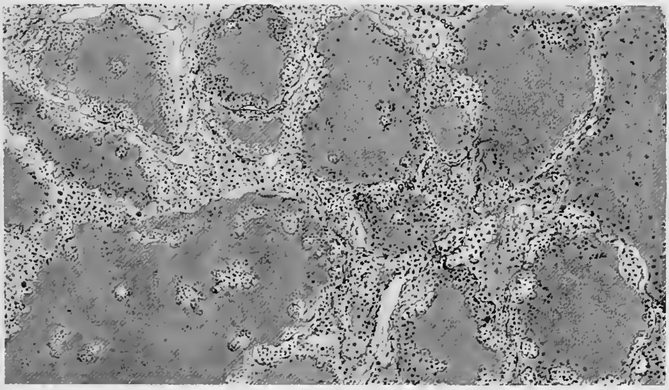

FIG. 1.—Microscopic drawing of a colloid adenoma.

The illustration shows that the thyroid vesicles are distended with a homogeneous colloid substance in which are clumps of epithelium and isolated epithelial cells.

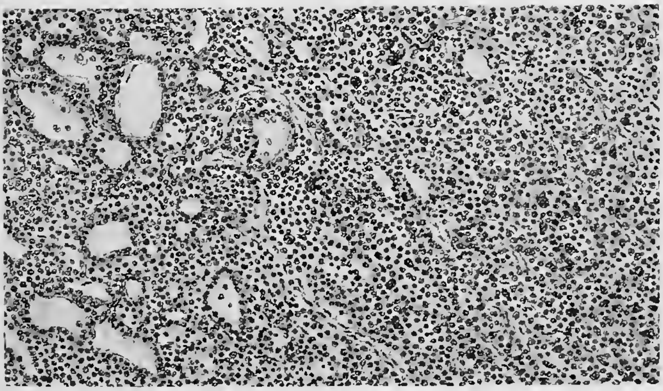

FIG. 2.—Microscopic drawing of a recurrent adenoma 4 oc., 3 obj., Leitz.

The left portion of the drawing shows tissue containing a few apparently normal thyroid vesicles. The right portion shows tissue in which no normal vesicles are present, but composed of epithelial cells, having no typical arrangement, and in a few of which a large, irregular, and deep staining nucleus is seen.

the thyroid five years ago, two years after her last child was born, and has gradually increased in size since. Dyspnœa has been more marked of late.

Operation, January, 1905, by Dr. Elting. Ether. "The patient took the anæsthetic very badly. Resuscitation was necessary during the operation. The tumor was removed through an incision along the anterior border of the right sterno-cleidomastoid muscle."

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated tumor measuring 2.5x2x1.5 cm., enclosed in a yellowish white capsule. On section it is fairly firm in consistence and presents a brownish white surface. Very little connective-tissue stroma can be seen.

Microscopic Examination.—Section shows a thick fibrous capsule with normal appearing thyroid tissue in its outer layer. The structure of thyroid gland can be made out, but the individual vesicles are small as a rule and contain no colloid. In a few areas the vesicles are elongated and assume a tortuous tubular shape. The connective tissue shows hyaline degeneration and œdema.

Microscopic Diagnosis.—Pure adenoma of the thyroid.

Etiology.—These adenomata comprise the solid non-malignant encapsulated tumors of the thyroid. They may arise within the tissue of the thyroid gland, without being connected with its capsule, or at some distance from the gland. They occur usually singly, but in two instances in my series they occurred as multiple tumors of one lobe. In one of these were present two smaller tumors, each about 3 cm. in diameter, attached to either pole of a larger tumor 8x3x3 cm. in size. In the other a tumor of the left lobe 8x6x3 cm. in size had attached to its capsule at one pole a small nodule about 2 cm. in diameter, which macroscopically had the same appearance as the larger tumor.

As to the location, five occurred within or apparently arose from the right lobe, two from the isthmus, and one from the left lobe, and in one instance the situation was not stated. These tumors are in my experience usually of small size. The largest was 10x8x6 cm. and the smallest 3 cm. The average diameter was about 5 or 6 cm.

Clinically the adenomata are not as a rule difficult to recognize. They are hard and firm, freely movable, and generally present no symptoms except tumor. By their pressure upon the trachea or œsophagus they may produce dyspnœa or dysphagia and in two instances the extreme nervousness of the patient was ascribed to such pressure. The age of onset seems to correspond to that of adenomata in other glands of the body, occurring during youth or early adult life, when glandular activities are at their height. The age of onset was generally between 16 and 35 years; five or over one-half between the twentieth and thirtieth years. From the fact that these tumors produce no subjective symptoms, and that their growth is as a rule slow, it is often many years before the patient seeks surgical relief. It is probable that these tumors are far more common than indicated by this series, for it is only when they produce pressure symptoms or cause considerable disfigurement that the advice of the surgeon is sought.

No important etiologic factors, other than the age, can be determined. In one case, the tumor appeared two weeks after confinement.

There is nothing in the records to indicate that the thyroid gland in these cases was abnormal. Where observations were made by the operator, it is noted that the gland appeared normal.

Pathology.—The adenomata are definitely encapsulated tumors, usually smooth, but occasionally somewhat nodular or lobulated. The tumors vary considerably in consistence but are usually soft.

Two distinct varieties may be recognized, depending upon the type of vesicle. In the first, which we may designate as *pure adenoma,* the growth is found to be composed of closely-packed epithelial vesicles, containing little or no colloid and very small amount of connective tissue. Many of the acini are seen to be filled with epithelial cells. In the other variety, we have a condition in which histologically the picture very closely simulates that of simple hypertrophy. These we may designate as *colloid adenomata.* The epithelial vesicles are dilated and filled with colloid material. There is usually but a single lining layer of epithelium.

An interesting feature of these tumors is their tendency to undergo various degenerative changes. The colloid adenoma resembles somewhat histologically the simple hypertrophy, but differs, however, in some important respects. Thus the stroma is less abundant, the walls of the vesicles are thinner, and the epithelial cells lining the vesicles in the hypertrophied organ are of a lower type than those in the colloid adenoma. To make a distinction between simple hypertrophy and adenoma is easy clinically and from a macroscopic examination of the specimen, but upon histologic examination distinct differences in structure are not so evident.

Briefly stated, the main differences seem to be these:

(*a*) As to the epithelium lining the vesicles. In the adenoma we find the cell tending to a columnar character, while in the hypertrophy the cells appear more compressed and assume the appearance of a cuboidal type.

(*b*) As to the contents. Colloid. In the early adenoma, epithelial tissue is the one tissue present. Small amounts of colloid are visible, but this is not seen in appreciable amounts until a later stage. In this later stage the colloid is increased markedly in amount, and approaches as to quantity the amount which is visible in the hypertrophied gland. Besides this colloid material, which in certain amounts is normally present, the alveoli may also contain desquamated epithelium and red-blood cells. In the colloid adenoma there is usually present a large number of epithelial cells within the alveolus, which stands in marked contrast to the hypertrophy where no desquamation is evident. Again in the adenoma small hæmorrhages into the alveoli are more common.

(*c*) As to the stroma. In the adenoma scarcely any connective tissue stroma is visible, the vesicles with or without colloid material being closely packed together. In the hypertrophy, however, while a number of vesicles containing considerable colloid are in close proximity, being separated by small amounts of connective tissue, the groups of vesicles are isolated and between these groups dense and rather large amounts of connective tissue are visible.

Depending upon the secretory activity of the epithelial cells of the adenomata, a complex picture may be produced.

First, All of the epithelial cells may begin to secrete actively and varying amounts of colloid may appear within the alveolus, producing the *colloid adenoma.*

Second, All the epithelial cells may fail to secrete, and then we have a type of gland in which no colloid material is visible, resembling in many respects the type of tumor described as *fœtal* adenoma but differing in that the vesicle is not solid—*i. e.*, made up of several layers of epithelial cells, but is merely an alveolus lined by a single layer of cells in which no colloid material is evident.

Third, A number of the cells may remain dormant while the remainder are secreting colloid material, thus presenting the picture which many authors describe as *mixed adenoma.*

Cyst Formations.—Here I wish to emphasize the fact that undoubtedly a large percentage of cysts of the thyroid have their origin in adenomata. Very frequently we find in the walls of cysts thyroid tissue resembling simple hypertrophy. Cyst formations however in thyroids that have undergone simple hypertrophy is an extremely rare occurrence. None of the cases reported in this series show aught but minute cysts formed by the rupture of the walls of a few adjacent vesicles and the coalescence of their contained colloid. The adenomata, however, appear very prone to undergo degeneration with the formation of cysts. In Case VI it was seen that the tumor presented distinct evidences at its center of beginning cystic formation.

III.—Recurrent Adenoma. Three Cases—Male 2, Female 1.

The adenomata, as has been shown in the preceding section, occur singly as a rule and do not present histologically or clinically signs of malignancy. We have, however, three cases in which there has been either recurrence at the site of operation or a subsequent appearance of a similar tumor in other portions of the gland. These were clinically considered to be malignant, and the microscopic study revealed a more or less atypical growth of epithelium.

Case IX.—(Path. Nos. 97-3 and 64-19.) Male, aged 49. Thyroid tumor appeared twenty years ago and gradually increased in size up to five years ago, causing dyspnœa and dysphagia.

Operation, February 6, 1897, by Dr. Macdonald. Removal of tumor. Five months later a similar tumor appeared in the isthmus and gradually increased in size for four and a half years; and now presents as a firm apparently encapsulated tumor in median line of neck about 4x6 cm. in size. The lateral lobes of the thyroid show slight enlargement. The surgeon, Dr. Macdonald, considered the growth to be malignant and the entire gland was therefore removed.

Pathology.—(First operation.) Macroscopic Examination: Specimen consists of a portion of the thyroid gland measuring 9x6 cm. The outer surface presents a mottled appearance, the prevailing color being red, with here and there small areas of discoloration due to hæmorrhage. The surface vessels are distended. On section the specimen shows a large empty cyst, the walls of which are thin and covered by gelatinous substance, probably colloid material. Other cysts are seen of smaller size than the one just described. They are filled with a colloid material and in some are small pea-sized hæmorrhages. Portions of the growth have undergone calcareous degeneration.

Microscopic Examination.—No definite capsule is seen. The tumor proper is made up of tissue of the same general type as that of the normal thyroid but which shows greater irregularity in the gland acini. The connective-tissue network is moderately augmented; this is evident in the size of the strands. Irregularly distributed throughout the specimen are collections of epithelial cells of the same appearance as those constituting the normal gland structure. The gland spaces are for the most part smaller than normal, though here and there dilated spaces may be seen. All alveoli contain homogeneous pink-staining material, presumably colloid; in a few hæmorrhage has occurred. There is marked hyperplasia of the epithelial cells.

Microscopic Diagnosis.—Adenomatous cysts of the thyroid.

Second Operation.—(Path. No. 64-19.) Macroscopic Examination: Specimen consists of six pieces of tissue which are evidently from the thyroid gland. The largest portion measures 7x8x4 cm. Its outer surface presents a somewhat lobulated appearance and is covered with a smooth membrane to which are attached a few fibrous adhesions. Beneath the membrane the color of the tissue is a light red. On section the tissue is of fairly firm consistence, but varies somewhat in character in the different portions. In some places it presents a semi-translucent grayish white appearance, in others it is darker in color and somewhat more opaque. Considerable portions of the specimen are made up of the colloid material. Here and there are definite calcareous deposits. In one of the smaller portions which measures 7x4x2 cm. the tissue resembles that already described except that an area about 3.5 cm. in diameter is definitely hæmorrhagic. The remaining pieces which compose the specimen are similar in structure to the portions described.

Microscopic Examinations.—We have here the same general type of tissue seen in the tumor removed five years previously. Some of the gland acini are greatly enlarged and filled with colloid material; others are small and have only a cellular content. The epithelium approaches the columnar type and in many places shows no typical arrangement.

Microscopic Diagnosis.—Adenoma of thyroid.

In this case the specimen first removed (97-3) is a cyst which has apparently arisen by degeneration of an adenoma, while the second growth (64-19) presenting the same characteristics clinically, was an adenoma. The significance of this in relation to cysts will be discussed under that heading.

Case X.—(Path. No. 64-26.) Female, aged 45. Tumor of right lobe which first appeared seventeen years ago (1888). After five years it reached the size of a lemon and was removed September, 1893, no pathologic study was made. Four years after first operation (1897) a similar tumor appeared in the left lobe and was recovered six years later (Sep. 21, 1903), by Dr. Macdonald. This tumor the patient states seemed exactly similar to the first one. Both finally produced pressure symptoms upon the trachea and œsophagus, and for relief of these symptoms patient sought operation. With the second tumor there was considerable pain, and dyspnœa and dysphagia were more pronounced. The description of this tumor follows:

Pathology.—Macroscopic Examination: Specimen consists of a portion of thyroid gland measuring approximately 11x4.5x3.5 cm. Beneath the capsule except in a small portion of the end of the tumor can be seen numerous pea to cherry-sized cysts. In the center of the specimen can be felt a hard stone-like mass the size of a cherry. On section all but a small area at one end of the specimen is seen to be filled with various sized cysts containing a clear colloid material. The wall of one of the larger cysts is completely calcified and measures 2 mm. in thickness.

Microscopic Examination.—The gland alveoli are numerous and for the most part distended by homogeneous colloid material. Some contain also desquamated cells and leucocytes many of which are loaded with pigment. The alveoli surrounding the more distended alveoli are small and arranged concentrically. Other areas show small irregularly developed alveoli. Several are irregular and without any distinct limiting wall and contain a bluish pink mucoid-like material, blood pigment and elongated connective-tissue nuclei. The interalveolar tissue shows hyaline degeneration in places.

Microscopic Diagnosis.—Adenoma with hæmorrhage and calcification and a tendency to an atypical growth of the epithelium.

About two months ago, two years after the second operation, a tumor appeared in median line of the neck and has slowly increased in size. This tumor is clinically an adenoma. There is no evidence of recurrence at the sites of previous operations. Patient's general health is excellent. The patient is considering an operation.

Case XI.—(Path. No. 97-2.) Male, aged 60. Tumor removed from the region of the right lobe of the thyroid by Dr. Macdonald nine years ago.

Pathology.—Macroscopic Examination: Specimen consists of a mass almost the exact size and shape of a kidney. The surface is irregular and in places it is covered by a distinct capsule which is somewhat hæmorrhagic. In other places patches of connective tissue containing large blood-vessels lie on the surface. It is somewhat lobulated and of a brownish yellow color. On section at one point is seen a cyst-like cavity containing a friable grumous material of a yellowish color, slightly viscid and apparently cell-detritus. The remainder of the tumor can be divided into a cortical and medullary portion. The cortical portion averages about 1.5 cm. in width and is distinguished from the medullary by its light color and more or less radial striation due to the presence in its substance of fine bands of connective tissue. The medullary substance is distinctly pinker in color than the cortical, and the bands of connective tissue which traverse it have no distinct or regular distribution. The consistence of the tumor as a whole is firm, the cortical substance perhaps being a little firmer. Distinct areas of calcification are present.

Microscopic Examination.—(See Fig. II.) Sections show the tumor to consist of a capsule and tumor substance. The capsule is for the most part made up of fibrous tissue. Here and there, however, it contains small collections of cells of the same type as the gland-cells, and it is evidently formed of compressed gland substance. The tumor itself is composed of a tissue of the same general type as normal thyroid tissue. It differs in the greater irregularity and shape of the gland acini. Near the capsule the connective-tissue network often runs in parallel striæ passing from the capsule into the depths. In the deeper parts of the tumor this cannot be made out. The colloid material in one or two places has undergone calcification.

Microscopic Diagnosis.—Adenoma of the thyroid.

Recurrence in same location after seven years. This second growth was an encapsulated tumor which had reached the size of a hen's egg. Specimen not saved for pathologic study.

A year after the removal of the second growth (April, 1903) there was again a recurrence which soon reached considerable size. On consulting a surgeon at this time the process was considered malignant and operation not advised. From this time until January, 1906, about one and one-half years, when patient was last seen, there has been constant increase in the size of the primary growth, which now measures 7x6 cm. in size. It is located in the right lobe of the thyroid and extends apparently deep into the neck. Near the upper pole of this tumor there is a second mass, which made its appearance about one year ago. This is entirely distinct from the older tumor, is superficial, and has no deep attachments. It is ovoid in shape, 5x4 cm. in size, and moves about freely underneath skin, which is nowhere adherent over either tumor. Patient has thus far refused operation.

We have then in this case a thyroid tumor which has returned twice after removal, the condition extending in all over a period of nine years, and in which there has developed now in the region of the recurrent tumor a secondary growth. The patient is still in fair general health but suffers from the effects of pressure. The question of carcinoma arises. The long duration would almost exclude this possibility. The growth, while of large size, is as far as can be determined, encapsulated, and affects the health of the patient only by its mechanical presence. Histologically, the first growth removed can be characterized only as an adenoma, though it does present an unusual picture, similar to that in the other two cases described in this group. An interesting feature is that in all of these cases the patients are now over 40 years of age. In one the onset of the first growth was at 51 and in the other two, one at 29 and the other at 32 years of age, thus differing from the usual history of adenoma.

IV.—CYSTS. 12 CASES.

No.	Age of onset.	Age at operation.	Duration.
1	10	16	6 years.
2	21	26	5 years.
3		27	
4	17	26	9 years.
5	38	42	4 years.
6	33	41	8 years.
7	36	43	7 years.
8	15	24	9 years.
9	25	33	8 years.
10	19	20	18 months.
11	49	49	4 months.
12	39	43	4 years.

Average age of onset, 27 years and 6 months; average age at operation, 32 years and 6 months; average duration of disease, 6 years; females 7, males 3; sex not stated 2.

We recognize three main types of thyroid cysts, *simple, hæmorrhagic,* and *adenomatous cysts.*[1]

Simple Cysts.—Three cases.

CASE XII.—(Path. No. 06-197.) Male, aged 16 years. When six years of age his parents noticed a small lump about the size of a hickory-nut in the region of the left lobe of the thyroid. This increased very little in size until four years ago, since which time there has been slow but gradual enlargement. There is no exophthalmus or tremor, but the boy is of a nervous disposition.

Operation, January 22, 1905, by Dr. Beilby. Anæsthetic, cocaine. In the region of the left lobe of the thyroid is found a smooth ovoid tumor about 5x9 cm. with its larger diameter extending from the thyroid cartilage towards the ear. No lobulations can be made out. The tumor is very tense and no definite fluctuation can be determined. It is attached to the larynx and moves up and down perceptibly on swallowing. The cyst was excised without rupture. The thyroid tissue about the cyst appears normal.

Pathology.—Macroscopic Examination: Specimen consists of a cyst of the thyroid gland measuring about 6x9 cm. in size. Its outer surface is smooth and only at the pole can thyroid tissue be seen. On opening the cyst the walls are found to be very thick and fibrous. The contents of the cyst is a brownish translucent fluid with numerous oil-globules floating about in it. The inner surface of the cyst-wall is very white and fibrous and is covered with many flakes of fibrin and some atheromatous patches. One small area of the thyroid tissue 1x1.5 cm. projects from the inner wall of the cyst.

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[1] In addition to these, occur the small multiple cysts found with great frequency in the simple hypertrophic gland. They never attain any great size and are undoubtedly caused by the coalescence of two or more distended vesicles with fusion of their colloid contents. Clinically, they never produce any symptoms and are only of pathologic interest.

Microscopic Examination.—Cyst-wall: outer layer of loose fibrous connective tissue with blood-vessels and a very cellular central zone. At first glance these cells look like lymphoid cells, but the presence here and there of small amounts of colloid material leads to the conclusion that they represent greatly compressed thyroid vesicles with atrophied epithelium. The next layer is the inner wall of the cyst, which is composed of loose lamellæ of tissue and masses of blood-corpuscles, suggesting an organized blood clot.

Microscopic Diagnosis.—Simple cyst of thyroid.

At present, one year after operation, patient is perfectly well.

This is the type of a thin-walled cyst. They occur in glands that are apparently normal. The cyst-wall is composed of compressed thyroid tissue. The inner wall is usually smooth and fibrous but may be lined with a mass of epithelial cells. The contents is usually fluid but varies both in color and consistence, the color depending on the amount of blood and the consistence on the admixture of colloid.

Hæmorrhagic Cysts. One case.

The following case illustrating this type, is perhaps almost unique.

Case XIII.—(Path. No. 195.) Male, aged 41. Eight years ago patient fell backward down stairs. Noticed at once, following the fall, a swelling in the region of the right lobe of the thyroid gland. This increased in size but little until a few days previous to operation, when a rapid enlargement occurred. This was accompanied by a constant dull pain for which the patient sought advice.

Operation, March 16, 1904, by Dr. Elting. Nitrous oxide and ether. Excision of the right lobe of the thyroid. 50 c.c. of brownish fluid was evacuated from the cyst during its removal.

Pathology.—Macroscopic Examination: Specimen consists of an encapsulated mass, evidently comprising the entire right lobe of the thyroid gland. It measures 10x5x4 cm. On section a large cavity is found from which was evacuated 50 c.c. of reddish brown fluid containing necrotic tissue. The necrotic material is both free in the cavity and adherent to the walls of the cyst. Here and there in the walls are found calcified areas, none larger than 5 mm. in diameter. The wall of the cyst averages about 5 or 6 mm. in thickness.

Microscopic Examination.—Sections show the cyst-wall to be composed of thyroid tissue, in general fibrous, but in some areas quite normal. There are areas of hemorrhage and necrosis. In these areas and surrounding them is an extensive infiltration with polynuclear leucocytes, though in general the tissue is infiltrated with lymphoid—and plasma-cells. The picture everywhere presented is that of chronic inflammation with tissue degeneration and focal areas of necrosis. The type of thyroid vesicle where it can be made out is that of the normal gland.

Microscopic Diagnosis.—Hæmorrhagic cyst with chronic thyroiditis, hæmorrhage and necrosis.

Hæmorrhage has always been assigned as an important factor in the production of thyroid cysts. The presence of hæmorrhage, recent or old, in cyst contents or its walls is an almost constant observation. It seems probable, however, that this is much more commonly a secondary process than the true etiologic factor. That a primary hæmorrhage, produced either by violent trauma, or the rupture of a small blood-vessel from any cause within the substance of the thyroid gland, is capable of producing later a cyst there can be no doubt.

Adenomatous Cysts.—Ten cases.

That the adenomata play such an important rôle in the production of cysts seems not to have been generally recognized. In this series, 70 per cent., or 10 of the 14 cases, present evidence of having arisen from this type of tumor.

CASE XIV.—(Path. No. 05–010.) Female, aged 26. Tumor of neck nine years, gradual increase in size, more rapid during the last year. Dyspnœa and tachycardia on exertion. Pulse constantly 104–106. Marked harshness of voice. Complains of headache and pain in right ear. Tumor is situated in median line and moves with deglutition.

Operation, July 17, 1905, by Dr. Beilby. Cocaine. Transverse incision. Excision of cyst of isthmus. The remainder of the thyroid gland appeared normal.

Pathology.—Macroscopic Examination: Specimen consists of a thick walled cyst of the thyroid which was removed at operation without rupture. It is nearly globular in shape but slightly flattened in its anterior-posterior diameter. It measures 7.5x5.5 cm. Its capsule is of a pink color, very delicate and easily torn. The blood-vessels are large and tortuous. It is rather soft and fluctuant. On section it is found to contain a brownish bloody fluid. This cavity is approximately 4.5x3 cm. in size. The wall of this cyst measures from 5 to 15 mm. in thickness and seems for the most part to be composed of apparently normal thyroid tissue. There are some areas, however, which resemble glandular hyperplasia. Again other areas show hæmorrhage and necrosis. Blood-vessels are large and numerous.

Microscopic Examination.—Section through cyst-wall shows a thick capsule, which has apparently been formed by compression of thyroid tissue. Scattered throughout are many normal thyroid cells and in some areas are acini filled with colloid material and lined with cuboidal epithelium. From this capsule strands of connective tissue extend to the deeper portion of the cyst wall and form a definite connective-tissue framework, presenting somewhat the histologic structure of thyroid acini. These spaces, however, are packed with what are apparently desquamated epithelial cells. A few normal acini are noticed, which are filled with colloid material. Other sections show in addition free masses of red-blood corpuscles, and marked hyaline degeneration of the connective tissue.

Microscopic Diagnosis.—Cyst in a *mixed adenoma.*

At present, eight months after operation, the patient is in excellent health. The huskiness of her voice has largely disappeared, her pulse has dropped ten to twelve beats per minute, and she is not so nervous as before operation.

Case XV.—(Path. No. 64-23.) Female, aged 26. Has had a tumor in the right side of the neck in the region of the thyroid for five years. Tumor first appeared during first pregnancy. There has been a gradual slow increase in size up to three years ago, when after the birth of her second child the growth became more rapid.

Pathology.—Macroscopic Examination: Specimen consists of a globular cystic mass 5x3.3x2.5 cm., the outer surface of which is smooth and encapsulated. On section the cyst contents are found to consist of a brownish fluid. The cyst wall is smooth. The cyst originates in the thyroid gland, and to its outer surface fragments of normal thyroid-tissue are adherent.

Microscopic Examination.—The capsule is composed apparently of compressed thyroid alveoli. Within the capsule proper the tissue has the structure of thyroid and very slightly approaches the characteristic fœtal type of gland. No colloid is visible.

Microscopic Diagnosis.—Cyst in a pure adenoma.

Case XVI.—(Path. No. 97-4.) Female, aged 20; has had a tumor in the region of the isthmus of the thyroid for eighteen months.

Operation, October 19, 1897, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an oval piece of tissue 4.5x3.5x2.5 cm. It is for the most part cystic, the cystic contents having been removed, leaving a cavity which occupies about two-thirds of the tumor, the upper third consisting of a solid mass of tissue. The outer surface of the tumor is moderately smooth, but here and there are the remains of adhesions. The cyst-cavity is the size of a walnut and its walls are thin, averaging about 1 mm. in thickness. The inner surface is very irregular, and is traversed here and there by raised bands. The color varies from pinkish to grayish white. Secondary cysts varying from those the size of a pin-head to those the size of a pea can be made out in the walls. They contain a mucilaginous yellowish-brown fluid. In places on the inner surface of the cavity are areas of calcareous deposit. The solid portion of the tumor is only moderately firm in consistency and measures 2x1 cm. Its cut surface is of a yellowish gelatinous appearance. It contains a number of small cysts filled with fluid, which varies in color from a light to a dark brown.

Microscopic Examination.—The tumor on section presents varying appearances. In some places it has the ordinary appearance of thyroid gland structures, being made up of cavities of various sizes, containing colloid material, between which are cellular bands of tissue. This appearance is confined particularly to the portion of the tumor furthest removed from the cyst cavity. The walls of the cyst cavity are made up for the most part, of a firm solid tissue, composed of a basement substance containing numerous epithelial and spindle shaped cells. In this substance are to be seen the compressed remains of the thyroid alveoli and also a very large number of cells containing a yellowish brown pigment, evidently changed blood-pigment. At one point are present in the tumor a number of wedge-shaped spaces, the walls of which are formed by the tumor-tissue. In these are occasional spaces representing a deposit of crystals, presumably cholesterin. The cells about these spaces are multinucleated, apparently foreign-body giant-cells.

Microscopic Diagnosis.—Cyst in a colloid adenoma.

It will be recalled that in discussing the adenomata we recognized two types of thyroid vesicles—one large and containing colloid, and the other smaller in which no colloid was visible; also a third variety, combining the characteristics of these two. In the walls of these cysts we find a histologic structure which exactly corresponds to one or the other of these types. As we might perhaps expect, the colloid adenoma is the variety which most frequently undergoes cystic degeneration. Five, or one-half, of the cysts in this series were of this type. In only one could no colloid be seen in the tissue of the cyst-wall. Four were of the mixed variety. Aside from the histologic evidence of the production of cysts from solid adenomata, we have in certain of the cases a gross appearance indicating beyond doubt that the tumor was originally an adenoma and that degeneration has taken place with a resulting cyst formation. Of importance in this connection is the observation of cholesterin crystals indicating fatty transformation of the epithelial elements. If the process is an early one the cysts may be only of small size and the structure of the adenoma still be retained.

As the degeneration advances and the fluid contents of the cyst is increased in amount, there is compression of the alveoli and later many of the cells may atrophy and the stroma undergo various forms of degeneration, giving widely varying and very complex pictures. The inner layer of the cyst may then be said to be composed of the remains of the adenomatous tissue, while the wall proper represents the fibrous capsule of the original adenoma, and the outer layer, the stroma and compressed alveoli of the surrounding thyroid-tissue. With the enlargement of the cyst and its encroachment upon the surrounding normal thyroid-tissue we often get a lamellated appearance. These lamella are as the result of the successive compressions of the normal gland-tissue, with subsequent atrophy of the epithelial structures, leaving only the stroma and alveolar walls. Thus fibrous bands of varying thickness appear. Between these layers are often seen normal thyroid vesicles, and vesicles in various stages of atrophy.

The histogenesis of these cysts may be said to be as follows: In the beginning we have an encapsulated adenoma composed of cells which present no colloid secretion. As the growth continues colloid material is secreted and a coalescence of these colloid vesicles in the center of the tumor is to be seen. Hæmorrhage occurs and we have a cystic cavity filled with bloody colloid material. The fibrous capsule of the original adenoma forms the wall of the newly-formed cyst. As the degenerative process continues and the contents of the cyst increases the tumor necessarily becomes larger and pressure is exerted on the surrounding normal tissue, causing atrophy of apparently normal vesicles. As in long continued degenerative processes occurring in other tissues, lime salts may eventually be deposited in the wall of the cyst, giving extensive calcified areas.

V.—ABERRANT OR METASTATIC THYROID TUMORS WHICH ARE HISTOLOGICALLY BENIGN BUT CLINICALLY MALIGNANT.

ONE CASE.

CASE XVII.—(Path. No. 88-68.) Male, aged 65 years. Family and past history not important. Six months ago first noticed a fullness of right side of face and difficulty in breathing through right nostril. Tumor has increased in size rapidly and has been accompanied by considerable pain. At present there is complete occlusion of the right nostril and bulging of right eyeball with inflammation of conjunctiva, and obstruction of tear duct. At the operation by Dr. Vander Veer the antrum of Highmore was opened but only a small portion of the growth was removed. Its extensive character made a complete removal impossible. The clinical diagnosis was sarcoma of antrum.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of tissue removed from the upper jaw. There are one or two pieces of bone, the remainder of the tissue being of a grayish white color and having the appearance of granulation tissue.

Microscopic Examination.—The sections indicate that the tissue is that of the thyroid. Two definite pictures are presented. First, large alveoli filled with colloid, lined usually by a single layer of cubical epithelium, and containing throughout the colloid substance many desquamated epithelial cells which take the stain rather poorly. Second, areas showing epithelial hyperplasia but less tendency to colloid secretion, giving the tissue a more solid cellular appearance. On careful examination of these cellular areas they are found to be composed of closely packed thyroid vesicles, some of fair size but filed with cells which approach a columnar type. Hæmorrhages into the alveoli are frequent. Connective tissue stroma is very scant. The tissue shows signs of inflammation in places, containing a number of polynuclear leucocytes.

Microscopic Diagnosis.—Aberrant or metastatic thyroid tumor.

For the further history of the case I am indebted to Dr. Merritt, of Cherry Valley, who writes me that the growth increased very rapidly after the patient left the hospital and finally involved the right eye. The bony structures he thinks were extensively involved as some of the teeth and a portion of the superior maxilla were lost during the course of the disease. To the best of the doctor's recollection and that of the patient's friends, there was no hypertrophy or tumor of the thyroid gland, either previous or subsequent to operation.

To establish a positive diagnosis of *metastatic adenoma of the thyroid,* we must necessarily have at least clinical evidence that a primary adenoma existed in the thyroid gland. This evidence is wanting. If such an adenoma existed it was so small as to escape notice. Whether or not such a primary tumor existed the case is of equal interest.

There are now in the literature records of about 20 cases of tumors apparently metastases from the thyroid, which were histologically benign. As in a number of these instances there has been no apparent primary thyroid lesion, these cases have been considered as *metastases from normal thyroid tissue.* Where a thyroid lesion has been observed it has been that of simple hypertrophy or adenoma, and the metastatic tumor has had a similar histologic structure. These metastases, which may be single or multiple, have occurred most frequently in bone, and have often been removed under the supposition that they were primary growths. Aside from the fact that these tumors are probably of metastatic origin, they present as a rule no other indication of malignancy. Frequently, however, they have been known to recur after removal and a number of cases have thus resulted fatally. Therefore the important question arises, are not these tumors malignant and should they not always be considered as such by the surgeon?

In the case I report the tumor presented clinically every indication of malignancy. Its invasion of tissue was rapid and death was caused in eight months after its onset. As there never was observed any hypertrophy or tumor of the thyroid gland, we can only assume that if this was a metastatic tumor the metastasis was from normal thyroid tissue. As will be noted, however, in the microscopic study, the growth was histologically a thyroid adenoma and of the type we have described as mixed adenoma.

In the case reported by Oderfeld and Steinhaus[1] the first tumor observed was in the frontal bone. This was removed and histologically found to have the structure of normal thyroid. The patient was again seen after an interval of six months, but no recurrence was evident. After about a year there was a recurrence and also other similar tumors made their appearance, one in the temporal region and one at the sterno-clavicular articulation. Clinically these tumors were considered to be malignant. At the request of the patient the one in the temporal region was removed. This presented a similar structure to the one removed from the forehead one year before. The patient died a few weeks later. Before death a thickening of the under half of the right lobe of the thyroid was noted. A complete autopsy was not permitted, but all visible tumors were removed together with the thyroid gland. Within the substance of the right lobe of the thyroid was found a small nodular thickening 2 cm. in diameter. The remainder of the thyroid appeared normal. The tissues were all carefully sectioned and examined, the authors expecting to find carcinomatous degeneration, but the structure throughout the tumor of the thyroid and the other isolated tumors of the head and neck were uniformly the same, and as they observe had the exact structure of normal thyroid tissue. They regard the small thyroid nodule as the primary tumor and the tumors of the head and neck as metastases.

Etiology.—The fact that we have in these metastatic tumors structures similar or almost identical to the tissue found in the normal gland lends special interest in the etiology of these tumors. In its consideration several factors may be taken into account.

First, Origin from *misplaced embryonal tissue.* The theory which has been advanced by Conheim in which he regards the etiology of malignant growths as due to misplaced embryonic cells might be applied to tumors of this class.

Second, Origin from *aberrant or accessory thyroid.* Murphy in a recent article[2] calls special attention to a group of accessory thyroid glands which he frequently finds at the base of the tongue and which he classified as the superior group. He records

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[1] *Centralb. f. allg. Path. u. path. Anat.*, 1903, xiv, 84.

[2] *Jour. of the Amer. Med. Assoc.*, 1905, xlv, 1854.

39 cases. In only three is there a note upon the histology of the tumor. Two presented the appearance of "normal thyroid," and one of "colloid goitre." In six, or 15 per cent of the cases, there was recurrence after removal but no other signs of malignancy.

Third, *Propagation of bits of thyroid tissue through the circulatory system.* It is a well-known fact that certain tissues, especially young embryonal cartilage, when transplanted into different tissues of the body or when injected into the circulatory apparatus are apparently nourished and in certain instances continue to grow. An apparently analogous condition is true in regard to the thyroid-gland tissue. Portions of this gland have been excised and immediately transplanted into another animal of a foreign species. The tissue not only has remained alive but has apparently continued to produce its normal secretion. Although no proof is at hand, it is possible that these metastatic tumors could result from small particles of thyroid tissues which had found their way into the circulatory apparatus and had been transferred to distant portions of the body. In an organ as vascular as the thyroid such a condition is not inconceivable, especially under conditions of trauma.

As is well known metastases from tumors of the thyroid, like those of the prostate, occur most commonly in bony structures.

VI.—EXOPHTHALMIC HYPERTROPHY. SIX CASES. ALL FEMALES.

No.	Age of onset.	Age at operation.	Duration.
1	28	29	16 months.
2	25	26	1 year.
3	20	21	1 year.
4	24	27	3 years.
5	28	43	15 years.
6	44	46	2 years.

Average age of onset, 28; average age at operation, 32; average duration of disease, 3 years and 10 months.

Result.—In two cases death occurred, one (case No. 3) on the table at the end of operation as a result of the anæsthetic; the other (case No. 2) died seven days after operation, with the symptoms of extreme hyperthyroidization. The remaining four cases have been either entirely cured or greatly benefited by the operation. Case No. 1, four years after operation, is well and all the symptoms have been relieved except slight prominence of the eyes which remains. The portion of the gland that was left at operation is now distinctly palpable. Case No. 4, one year and two months after operation: the symptoms are all relieved and the patient is able to pursue his work. Before operation exophthalmus, tachycardia and nervousness were marked. Case No. 5 is well ten months after operation. Case No. 6: operation was done but one month ago. The condition of the patient is improved.

CASE XVIII.—(Path. No. 64–25.) Female, married, aged 26. Complains of enlargement of neck, poor sight and some difficulty in breathing. Onset one year ago; first symptom enlargement, followed by exophthalmus. Thyroid gland now presents symmetrical enlargement; exophthalmus very pronounced, marked tremor of hands. Systolic murmur heard over base of heart; not transmitted. Heart not enlarged. Pulse 140.

Operation, June 24, 1903, by Dr. A. Vander Veer. Ether anæsthesia. Both right and left lobes were removed. For three or four days after operation the pulse ranged between 130 and 158, temperature between 100 and 102° F. Delirious at intervals. Death on the seventh day.

Pathology.—The gross description merely contains the statement that the specimen consisted of two masses of glandular tissue, one measuring 8x4x2 cm. and the other 5x4x1.5 cm.

Microscopic Examination.—(See Fig. 3.) Sections 1, 2 and 3 all show the lobulated structure of the thyroid gland. There is an increase in the interlobular connective tissue. The vesicles composing the lobules are very irregular in size and shape. The colloid material in many of the vesicles has been entirely replaced by epithelial cells. Instead of a single layer of epithelium lining the individual vesicles, we see a number of layers, this proliferation of cells often producing invaginations or papillary projections into the cavity of the vesicle. In certain areas this proliferation of cells has advanced to such an extent as to completely fill the vesicle and we have entire lobules presenting a solid cellular structure. The cells are of a high columnar type. There is lymphocytic infiltration in areas.

Microscopic Diagnosis.—Advanced and diffuse exophthalmic hypertrophy.

CASE XIX.—(Path. No. 763.) Female, single, aged 21. Enlargement of thyroid for one year, more marked on right side. Exophthalmus, tremor and tachycardia pronounced. As patient steadily grew worse under medical treatment, operation was advised.

Operation, September 28, 1904, by Dr. Elting. Ether anæsthesia. Excision of right lobe and isthmus. Left lobe not removed. The patient died on the table at the end of operation.

Pathology.—Macroscopic Examination: Specimen consists of two pieces of tissue, measuring respectively 6x4.5x3 cm. and 3x2.5x2 cm. in size. Both are of similar structure. The larger is somewhat lobulated and is encapsulated except on one surface, near the upper pole, where there is a raw granular surface corresponding in diameter to the smaller piece. Both masses are more or less nodular and on section have a pinkish white granular appearance. There are several cysts 0.5 to 1 cm. in diameter containing straw-colored grumous fluid. The surface presents rather round or oval areas, each being somewhat distinct from the other.

Microscopic Examination.—The sections present an unusual picture for exophthalmic hypertrophy. They have in general a definite lobulated glandular appearance. In many lobules the proliferation of epithelial cells has progressed to such an extent as to entirely obliterate the characteristic thyroid gland structure, giving solid epithelial masses. The walls of the individual vesicles have disappeared, evidently as a result of pressure. In one such area (see Fig. 4) there is in addition an unusual change in the cell morphology. As seen in the microscopic drawing, the cells are very large and irregular in shape and in this regard suggest very strongly malignant transformation. In one section, evidently representing the wall of the small cyst mentioned above, the hypertrophy is not so far advanced and hyperplasia of the cells with papillary projection or invagination of the epithelial layers into the cavity of the vesicle is seen, representing more the picture we recognize as that of exophthalmic hypertrophy. The colloid material except in a few places has disappeared. In the study of these sections one is impressed with the possibility of the association of exophthalmic hypertrophy and carcinoma.

CASE XX.—(Path. No. 05–1376.) Female, single, aged 46. For six years headache, extreme nervousness and dizziness at irregular intervals. Two years ago onset of exophthalmus, tachycardia and tremor. Four months later observed enlargement of thyroid gland. This enlargement is symmetrical and well marked.

Note on physical examination.—Patient is a rather slightly built woman, rather poorly nourished and anæmic. Areas of discoloration of skin on left cheek and backs of both hands. Exophthalmus definite but not of an extreme degree. Sight has failed rapidly. Pulse regular, of even tension, 96 per minute. On admission to hospital it is recorded as 90. Thyroid gland shows a nearly symmetrical enlargement, left lobe a little larger than the right, measuring about 8.5x5 cm. and is moderately firm.

Operation, December 29, 1905, by Dr. Elting. Ether; excision of left lobe and isthmus.

Pathology.—Macroscopic Examination: Specimen consists of what is apparently the left lobe and a portion of the isthmus of the thyroid gland, which have been removed in one piece. The outer surface has a pinkish-yellow mottled appearance. It is covered by a rather delicate fibrous capsule, which has been torn in places and adheres by firm hair-like adhesions. The surface has a distinct lobulated appearance, the lobules varying in size from 0.5 to 2 cm. Several minute cysts 1 to 2 mm. in diameter are seen upon the surface. The tissue has a rather firm feel, and is very nodular. Section has been made through one area where near the surface a cyst has been opened. This cyst is 1.5 cm. in diameter and contains some thick, viscid, translucent material. On section the cut surface presents a reddish-yellow mottled appearance. Lobulations are definitely seen. These vary in size from 1 mm. to 1 cm. and are of

PLATE V.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

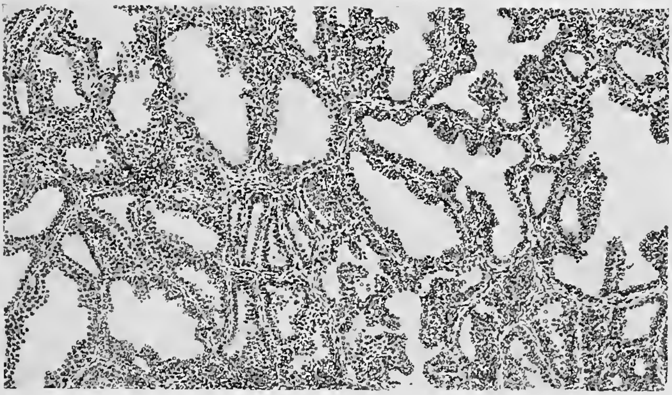

FIG. 3.—Microscopic drawing of an exophthalmic hypertrophy (exophthalmic goitre), 4 oc., 3 obj., Leitz.

In this drawing the hypertrophy is indicated by the proliferation of the epithelial cells lining the vesicles and the papillary projections into their lumen. In places some of the vesicles have been compressed by the hypertrophy of the surrounding epithelium.

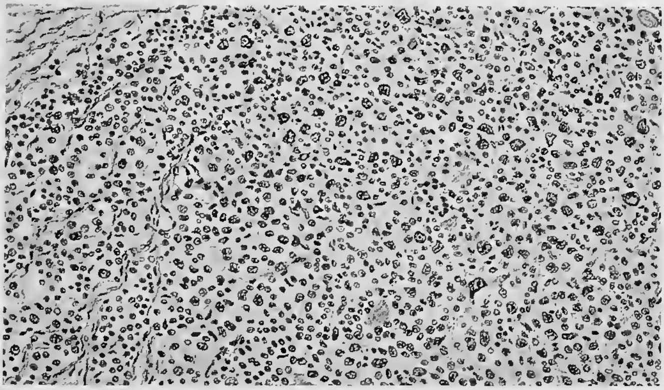

FIG. 4.—Microscopic drawing of a section of thyroid which presents in other areas a definite picture of exophthalmic hypertrophy, 4 oc., 3 obj., Leitz.

(See microscopic description.)

widely different shape. The connective-tissue surrounding the lobules can be seen as distinct white bands. It seems more abundant near the center and in the posterior part. Within the lobules can be seen minute translucent areas, which presumably are thyroid vesicles filled with colloid. The entire lobe as far as determined by section has this appearance. In the isthmus are areas of a more distinct red appearance. The lobules are firm and definite translucent areas cannot be seen. The appearance here approaches more nearly that of normal thyroid tissue.

Microscopic Examination.—A series of sections show two definite processes. There is seen to be in the majority of the sections a marked increase in the size of the alveoli and in the amount of colloid present. In certain lobules this is much more pronounced, and suggests a simple hypertrophy, differing perhaps only in the tendency of the cells to assume a higher type in many of these large colloid alveoli. In other areas there is cellular proliferation with diminution or disappearance of the colloid material. The increase in the number of epithelial cells is very great while their approach to the columnar type is not so marked. An alveolar arrangement is frequently difficult to make out. Section through the wall of the small cyst, noted above, shows it to be in the center of a minute encapsulated adenoma. The connective tissue of the gland is moderately increased in amount and there is considerable lymphocytic infiltration in areas.

It seems, then, that we may recognize two forms of exophthalmic hyperthrophy; in the one form the disease begins in an apparently normal gland and the process is symmetrical, so that histologically we find everywhere the type of lesion so well illustrated in Fig. 3. Clinically in this form we recognize as a rule a very symmetrical enlargement of the gland, though one which never attains great size. The disease is of comparatively short duration, patients dying as a rule in from one to three years if untreated. The well known symptom-complex of the disease,—enlargement of the gland with exophthalmus, tachycardia and tremor,—is invariably present. In the other form the exophthalmic process is secondary or associated with some other type of thyroid affection. In three, or one-half, the cases in this series an associated simple colloid hypertrophy was found. The cases in this series illustrating this type are Nos. 4, 5 and 6.

This form is characterized clinically by a longer duration, by a greater increase in the size of the gland, and by lesser severity of the symptoms. These cases, however, all had exophthalmus, tachycardia and nervousness of greater or lesser severity. In Case V, while the enlargement of the gland was of 15 years' duration, the symptoms of exophthalmic goitre had developed more recently. In the other two cases these symptoms were present from the onset.

The histologic picture also differs. Instead of a uniform process, as in the former group, we see the exophthalmic hypertrophy only in foci or in various lobules scattered throughout the gland. In the cases where this hypertrophy is observed it is of a lesser degree. Other investigators have also recently called attention to the fact that exophthalmic hypertrophy is frequently associated with various pathologic conditions of the thyroid, as cysts, adenomata and carcinomata, and that these may be the unproduced atypical exophthalmic goitre symptoms. Usually there is present the nervousness, tachycardia and tremor of varying degree while the symptoms of exophthalmus may be wanting.

In typical cases of exophthalmic goitre, which present the well-known symptom-complex, all writers agree that the histologic changes found in the gland are definite and constant. They have been characterized as a true hypertrophy. They very closely resemble the compensatory hypertrophy which is seen in the remaining portion of the thyroid gland after its partial excision, and which in this manner has been so frequently produced experimentally in dogs. Briefly the changes are (1) a change of the epithelium from a low or cuboidal type to a high cylindrical form, (2) a gradual disappearance of the colloid material which seems to be one of the earliest evidences of beginning hypertrophy, (3) alteration in the size and form of the alveoli due to the hyperplasia and infolding of the epithelium, (4) increase in the vascular supply and in the connective tissue stroma.

As we have noted, however, in cases in which symptoms are atypical no such definite changes are observed. We may see only in foci evidences of this process. It may amount simply to a change in the size and form of the cell, and perhaps instead of a single layer of epithelium lining the alveolus there may be two or more. There may be said to be, however, in all cases evidence of proliferation of cells with increased activity. Whether or not we shall be eventually forced to the conclusion that all the various affections of the thyroid gland characterized by cellular proliferation give rise to the symptoms, more or less complete, of Graves' disease is a matter which requires further study.

As to the pathogenesis of this affection nothing can be said to have been as yet definitely established. The main dispute is still whether the disease is of nervous origin or has its basis in an abnormal condition of the gland itself. The majority accept the latter view, and hold that the disease is a manifestation of an excessive or perverted secretion of the thyroid epithelium. This seems the most rational supposition and it is borne out by certain facts,—viz., the similarity in the histology of the compensatory hypertrophy and the exophthalmic variety; the relationship between the advancement of the hypertrophy and the duration and severity of the clinical symptoms; and the beneficial effects that are produced by removal of a portion of the hypertrophied gland. What relation if any the parathyroids have to exophthalmic goitre has not been determined. In none of these cases were these bodies examined. The changes that have been described are not at all constant.

In regard to the age of onset, the cases of this series correspond closely with those of other observers. By far the greatest number appear between the ages of 20 and 30, five out of six cases are recorded above. In one case, however, the age of onset was stated as 44. An onset before puberty or after 40 is rare. The disease is much more common in females than males, the proportion as variously stated ranging from 3 to 1 to 17 to 1.

VII.—Chronic Thyroiditis. One Case.

Case XXI.—(Autopsy No. 0-283.) Autopsy, April 18, 1900, by Dr. Blumer. Female, aged 40. No clinical history.

Anatomical Diagnosis.—Sclerodema with pigmentation of the skin affecting the face, posterior part of the trunk and extremities. Acute sero-fibrinous pericarditis, with acute myocarditis and diffuse interstitial myocarditis. Double hydrothorax with acute fibrinous pleurisy on the left side. Acute bronchitis with emphysema of the lungs and atelectasis of the lower lobes. Chronic passive congestion of the liver. Acute infectious nephritis. Chronic interstitial thyroiditis. Chronic interstitial mastitis. Tuberculosis of a bronchial lymph-gland. Small ulcers over the internal condyles of the humeri.

Pathology.—Macroscopic Examination: The thyroid gland is small, firmer and somewhat grayer in color than normal. It contains apparently an increased amount of connective tissue.

Microscopic Examination.—Marked changes in the gland are seen. These take the form of a great increase in the interstitial tissue of the organ, producing compression and atrophy of the glandular substance. The new-formed connective tissue is mostly in the form of a dense, fully-formed fibrous tissue, but there are areas in which the thyroid tissue is infiltrated with small, round, lymphoid cells, apparently representing a recent infiltration. There is an increase in the elastic tissue. The gland substance shows varying degrees of compression. In some places it has almost entirely disappeared over quite wide areas; in other places it is apparently but little affected. There is an abundance of colloid material in the slightly affected areas.

Microscopic Diagnosis.—Chronic interstitial thyroiditis.

This case is not introduced into this series to raise the question of the relation of the thyroid to the condition of scleroderma, but as a typical illustration of the pathologic changes produced in the gland by a chronic inflammatory process. Acute inflammation of the thyroid gland frequently occurs following acute general infections, as typhoid and the exanthemata. The chronic form is very often associated with other thyroid affections, the hypertrophies, cysts and tumors, and they present in varying degrees the condition here described.

VIII.—TUBERCULOSIS. TWO CASES. ONE MALE, ONE FEMALE.

No.	Age of onset.	Age at operation.	Duration.
1....................	40	42	2 years.
2....................	35	43	8 years.

In the first case the previous health of the patient was said to have been good, but death from pulmonary tuberculosis occurred six years after the operation. In the second case the history at about the time of the onset of the thyroid involvement suggested pulmonary tuberculosis. The patient now (two years after operation) is in good health and presents no evidences of active tuberculous disease in any organ.

CASE XXII.—(Path. No. 64-2.) This case I am able to report as tuberculosis of the thyroid only upon clinical evidence, as although the microscopic sections show tuberculosis granulation tissue no thyroid structure can be made out. The patient was a male, aged 42. The disease began two years before with a small "lump" in the region of the thyroid gland which gradually increased to the size of a walnut, suppurated and discharged spontaneously, leaving two small sinuses which have persisted for a year. At the operation by Dr. Macdonald the sinus tracts were found to lead down to the thyroid gland and they were excised together with the gland in one mass. Clinically, as recently related to me by the operator, the process had its origin in the thyroid gland.

Pathology.—Macroscopic Examination: The specimen consists of a piece of tissue about one-half the size of a hen's egg. It contains some tissue which is presumably thyroid gland, and leading into it from the surface of the specimen are two sinus tracts, the walls of which are extremely ragged and lined with yellowish purulent material. *Bacteriologic examination* fails to show tubercle bacilli.

Microscopic Examination.—No thyroid tissue is to be seen. The sec-

PLATE VI.

To Illustrate Dr. Beilby's Article on "Affections of the Thyroid Gland."

Albany Medical Annals, January, 1907.

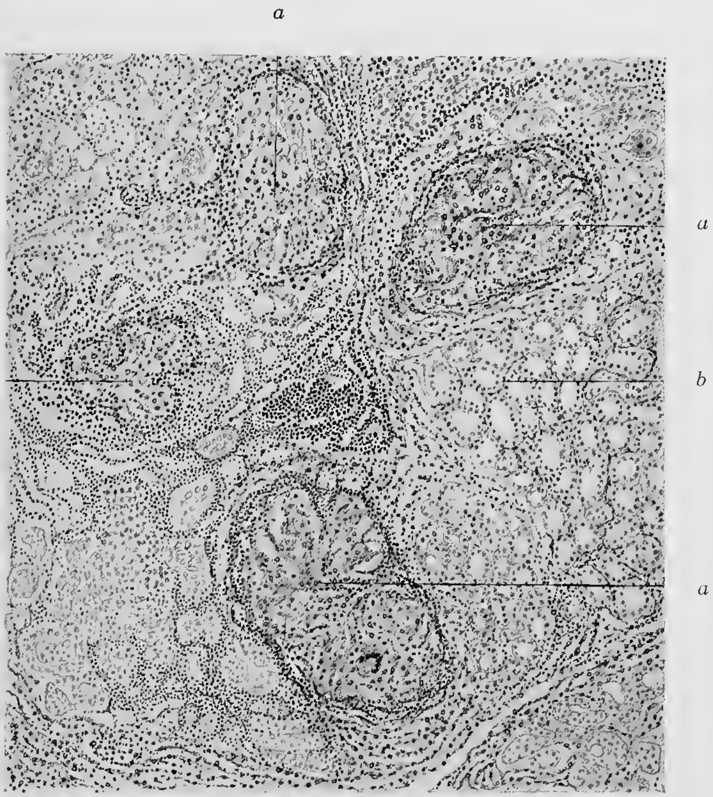

FIG. 5.—Microscopic drawing of tuberculosis of the thyroid gland, 4 oc., 3 obj., Leitz. (a) Tubercles, in the lower one of which is seen a giant cell. In the centre of the drawing, between the tubercles, is an area of lymphocytic infiltration. (b) Normal thyroid tissue.

tion consists of connective tissue and of large areas of caseation. Surrounding these areas of caseation is typical tuberculous granulation-tissue, made up of epithelioid and lymphoid cells, and containing an occasional giant cell.

CASE XXIII.—(Path. No. 64–21. History taken and physical examination made December, 1905, two years after operation.) Female, aged 45. When 14 years of age parents thought she had consumption; but, if so, she recovered completely. She married at 21 and now has 7 children, all in good health. At birth of last child, 11 years ago, she had puerperal fever and was seven months in bed. After this had a severe cough, night sweats and considerable expectoration. During this illness her physician first noticed a small tumor in the median line of the neck in the region of the thyroid gland which gradually increased till two years ago, when it reached the size of a hen's egg. It was tender on pressure and sometims painful and caused some dyspnœa during the last year before operation. It never showed redness or signs of inflammation. The patient entered hospital at this time for an operation for uterine myomata and she was persuaded by the surgeon to allow removal of this enlarged portion of thyroid.

Operation, November 5, 1903, by Dr. A. Vander Veer.

Pathology.—Macroscopic Examination: Specimen consists of an irregular mass of reddish brown tissue 6x4x2.5 cm., in which lies a sausage-like mass. This latter on section is found to be of a uniform consistency and of moderate firmness. Color is slate brown and deviating striæ give to the cut surface a lobulated appearance.

Microscopic Examination.—(See Fig. 5.) The thyroid tissue shows marked proliferation of alveoli, the majority of which are massed together, making the outlines of individual alveoli indistinct, while others contain a moderate amount of colloid material. In many of the lobules are circumscribed masses of epithelioid cells with occasional giant cells and a peripheral ring of lymphocytic infiltration. But a few of the tubercles show early caseation.

Microscopic Diagnosis.—Tuberculosis of the thyroid gland.

The patient was seen in December, 1905, 2 years after operation and this note on her present condition was made: "Patient is fairly well nourished, but slightly anæmic. There is a linear scar in the median line of neck 7.5 cm. in length, extending from a little beneath the chin to the episternal notch. Aside from a little thickening and redness at its lower end the scar appears healthy. There is no apparent enlargement of any portion of the thyroid gland. Patient has no cough and states that she is in good health and able to pursue her work. Examination of the lungs reveals no evidence of disease, though the breath sounds at both apices and considerably subdued. There is no glandular enlargement anywhere."

While it is true that tuberculosis of the thyroid gland is a rare disease, from recent studies it has been demonstrated that it is not so rare as was formerly supposed. Thus P. Bruns[1] in his report of 100 postmortem examinations made by Chiari of persons who had suffered from tuberculosis, states that the thyroid gland was involved in seven. Of these cases 96 had suffered from chronic pulmonary tuberculosis, and in only four of these was the thyroid gland involved; the other four were cases of acute miliary tuberculosis, and in three of these the gland showed involvement. Weigert in fifty cases of chronic pulmonary tuberculosis found tuberculosis of the thyroid in six. Two forms of involvement are recognized; a miliary form secondary to a general miliary tuberculosis, and a nodular form affecting the gland diffusely. The former is the more common. It does not produce any enlargement of the organ as a rule. Of the nodular form Bruns was able to collect six cases besides his own; in three of these from a clinical point of view the thyroid lesions were primary. This form is attended by enlargement of the organ sometimes sufficient to produce pressure symptoms. As illustrated in Fig. V, these tubercules have the ordinary characteristics of tubercles in other organs. They probably always arise in the interstitial connective tissue separating the vesicles.

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[1] *Beiträge zür klin. Chir.,* 1897, xi.

In the first case here recorded the data is so incomplete that no definite conclusions can be drawn. The clinical history states that the patient's previous health had been excellent, but there is no record of a physcal examination to exclude a possible pulmonary involvement. Then the fact that he is said to have died four years later of pulmonary tuberculosis leaves us in doubt as to whether the disease was primary in the thyroid with secondary involvement of the lungs or *vice versa*.

W. B. Stanton[1] has recently made the important observation that in a comparatvely large number of cases of pulmonary tuberculosis there were symptoms more or less complete of exophthalmic goitre and in these cases he has been led to examine the thyroid glands. The report is only a preliminary one and no cases in which he has observed these symptoms have died. He could not therefore give the results of histologic examination. Clinically there was slight thyroid enlargement. He records 26 cases of pulmonary tuberculosis aside from the above in which the thyroids were examined postmortem, but in which the patients were not examined clinically for those signs. In these, tubercles were found in four. As serial sections were not made he thinks it probable that the proportion found to contain tubercles is much too small. Further investigation of this point might yield informaton of great value.

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[1] American Medicine, 1905, x, 605.

IX.—CARCINOMA. ONE CASE.

CASE XXIV.—(Path. No. 98-43.) Female, aged 36, with history of illness for last three years. Prominent symptoms are enlargement of thyroid gland, with pain and anæmia. The patient was operated upon two years ago for thyroid enlargement, but no pathologic study of this specimen was made.

Second operation by Dr. A. Vander Veer, February 18, 1899.

Pathology.—Macroscopic Examination: Specimen consists of six masses of tissue, all roughly lobulated and varying in size from 6 to 3 cm. in greatest diameter. They all present similar appearances and are not distinctly encapsulated, though portions of capsule are here and there evident. Where a capsule is present it is generally smooth and of a yellowish-red color. The portions of the growth which are uncovered by capsule are finely lobulated, of a light yellowish-brown color, and have a translucent appearance. This appearance suggests, in some places, the appearance of thyroid-gland tissue; in other places it has a myxomatous character. On section the nodules differ in appearance; the smaller and presumably the younger ones have an almost homogeneous yellowish-gray cut surface, which is covered by sticky mucilaginous fluid which has the glistening appearance of mucoid tissue. In one or two of the smaller masses are areas of hæmorrhage. In one rather large area of light reddish-brown tissue which does not look like hæmorrhage, there is an area homogeneous in character and slightly granular. In two of the largest nodules near the center are areas of necrosis and calcification.

Microscopic Examination.—Sections from two different portions show an adenomatous tissue divided into irregular lobules by rather dense fibrous connective-tissue septa, which extend inward from a capsule which is present at one side. Except in a few small lobules near the periphery, where characteristic colloid-containing vesicles are seen, the tissue could not be recognized as thyroid-gland tissue. It is composed of papillomatous-like projections and long epithelial tubules with cavities of thyroid-gland spaces. This arrangement becomes complex and branching as the process develops, until they finally fill up the cavities, producing a gland-like appearance. The epithelium rests upon no visible basement-membrane; the stroma is very scanty. In the connective-tissue septa are many solid epithelial clumps which probably represent new foci of growth. A section from the homogeneous mass differs only in that no connective-tissue septa are seen, and the spaces are more closely packed with epithelial cells. This section also shows acute inflammation. The epithelial cell is of a high cylindrical type, varying greatly in size and shape.

Microscopic Diagnosis.—Adeno-carcinoma of thyroid gland.

From one observation of carcinoma of the thyroid no important deductions can be made except to call attention to its relative infrequency. One case in 61 thyroid affections, as indicated by this series is, however, undoubtedly too low a proportion and not borne out by the statistics from other sources. Bloodgood[1] in exactly twice the number of cases records seven of carcinoma. The most elaborate study of this condition that has appeared is by Ehrhardt,[2] who has collected 150 cases of carcinoma. Sixty-five of these occurred in men and eighty-five in women; 111 appeared between the ages of thirty and sixty. In over 50 per cent. of these cases it was definitely stated that a simple goitre preceded the development of the carcinoma, and in only a comparatively small number that it arose in a normal thyroid. This is the reverse of the condition seen in this country, probably due to the fact that we have no "goitrous districts," Ehrhardt recognizes three main varieties,—the medullary, which is the most frequent, the adeno-carcinoma, and the scirrhus. The latter is, in his experience, rare. Metastases occur early as a rule. In ninety-four bodies examined metastases were found in all but fourteen. In forty-six cases twenty-three had metastasized by the bloodstream alone, nine by the lymphatics alone, and fourteen by both these channels. As to the location of metastases, the lungs and bones are the most frequent seats. The bones of the skull and inferior maxilla are most commonly involved, though the sternum and long-pipe bones do not escape.

The average duration is about two years, the scirrhus form being the most chronic.

Clinical Diagnosis of Thyroid Affections.—When we bear in mind that the symmetrical enlargement of the thyroid gland indicates a hypertrophy, and the asymmetrical a tumor or a cyst, we have gone a great way towards making a diagnosis. To characterize all of the enlargements of the thyroid as "goitre" is obviously improper, as it conveys no intelligent clinical or pathologic meaning. If this term is used, it should apply to the hypertrophies, and we can then properly speak of the simple goitre and the exophthalmic goitre. To differentiate these latter conditions clinically is not difficult, for in exophthalmic goitre the subjective symptoms are definite and constant. In the simple form the rule is a much greater increase in the size of the gland but no symptoms except those produced locally by pressure. The age of onset and the duration of the disease are also important aids in diagnosis, as has been shown in the preceding tables. In the simple hypertrophy the age of onset in a large proportion of cases is before twenty. In an accurately recorded history I believe it would be exceptional to establish an onset after twenty-five. In the exophthalmic variety an onset before twenty is extremely rare; the majority of cases appear between the ages of twenty and thirty. The duration of the disease in the simple form is much longer, often twenty or thirty years, while that of the exophthalmic hypertrophy is usually less than two years. Where these two conditions are associated, or where the exophthalmic hypertrophy appears secondary to other thyroid affections, greater variation in these respects is seen. We must bear in mind that in either form of hypertrophy the process in one lobe may have advanced further than in the other, producing an asymmetrical enlargement, but on the other hand no part of the gland appears normal. In other words the process is a diffuse but not always an uniform one. Again, we have seen in certain cases a fairly symmetrical enlargement produced by an adenoma or cyst in either lateral lobe. These multiple tumors are comparatively rare, however, and on close examination present distinctive features. Of the tumors, the cysts and the adenomata are the most frequent, and they are often very difficult to differentiate. They both present the features of encapsulated tumors. The cysts are more apt to be smooth and ovoid in shape, while definite lobulations can often be made out in the adenomata. Variation in the size of the tumor seems to be frequent in the case of cysts. In regard to the recurrent adenomata, two of our observations at least would point to their being of a mild type of malignancy. Considering the long duration, however, and the fact that no metastases occurred, they do not present the features of carcinoma of the thyroid. In one case a secondary growth appeared in the region of the primary one.

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[1] *Surgery, Gynecology and Obstetrics*, 1905, i, 113.

[2] *Beiträge zür klin. Chir.*, 1902, xxxv 343.

From the fact that metastases of the thyroid tissue occurs in cases in which no primary tumors of the gland has been noted, bone tumors looked upon as primary should be approached with this possibility in mind.

Early diagnosis of the carcinomata presents the greatest difficulties and obviously is of the greatest importance. Age here is to be considered as indicated by the statistics of Ehrhardt. The disease is usually of short duration, a few months to one or two years. As met with in this country, carcinoma of the thyroid does not produce a large tumor, but it rapidly infiltrates the gland

and surrounding tissue and dyspnœa and dysphagia are early symptoms and out of proportion to the size of the growth. Change in the voice is also an early observation (Bloodgood). In districts where simple hypertrophy is endemic a very large proportion of the cases of carcinoma, as recorded by Ehrhardt, are secondary to this condition. Here the important feature is a sudden increase in size in the hypertrophied organ, with the return of symptoms after a quiescence of perhaps many years. Primary sarcoma of the thyroid is a rare affection and as no cases were observed in our series the condition will not be discussed.[1]

Treatment.—As the symptoms in the uncomplicated cases of simple hypertrophy and benign tumors are of a mechanical nature, the severity of these symptoms has been our guide in treatment. Rarely is operation undertaken for the relief of the deformity alone. I believe, however, that since so large a number of these cases undergo secondary changes in later life, making operation imperative, that they should be considered upon the same basis as similar lesions in other organs. In the case of the tumors and cysts an early operation is advocated. With the simple hypertrophy, if the patient has passed young adult life, the period when we might expect a subsidence of the process, and the gland continues to enlarge, a portion of it should be removed. If after a quiescent period new growth is observed, operation may be necessary for the relief of urgent pressure symptoms, and here, too, carcinoma must be considered. Scarcely fifty years have passed since Dieffenbach considered thyroidectomy a rash undertaking. To Kocher more than anyone else is due the credit of the advances in this field of surgery. At the German Surgical Congress, in 1900,[2] he reported the results of his second thousand cases of thyroidectomy, of which 929 were upon cases of simple hypertrophy and benign tumor. He had only four deaths, giving a mortality of 0.4 of 1 per cent. The greatest single factor contributing to this low mortality-rate was undoubtedly the substitution of local for general anæsthesia.

The general principles which guide us in the treatment of carcinoma of other organs should apply here, remembering that metastases occur early. Operation to effect a cure must be undertaken before there is extensive invasion of the surrounding tissues.

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[1] For report of cases and statistics see Lartigau (*Amer. Jour. Med. Sciences*, 1901, cxxii, 156).

[2] *Archiv. für klin. Chir.*, 1900, lxiv, 454.

In the treatment of exophthalmic goitre the various drugs and methods employed are almost innumerable. The weight of opinion now seems to favor partial thyroidectomy, and I believe justly so, for with the accumulating statistics the percentage of cures is increasing and the number of primary deaths decreasing. No other form of treatment has offered so much hope. The observations in this series have been made entirely on the operative treatment, but to give an opportunity for comparison I may be allowed to quote from a review of the literature made recently by the writer,[1] in which the results of some of the other more recent methods of treatment are recorded. In late years attempts have been made in many German clinics to develop a specific treatment of exophthalmic goitre. Lanz,[2] as early as 1894, began the use of the milk of thyroidectomized goats in patients with Graves's disease. He has recently recorded favorable results in five cases. Burghart and Blumenthal[3] in Leyden's clinic have injected the blood-serum of amyxo-œdematous patients into those suffering from exophthalmic goitre. Leyden reviews their results and thinks they are encouraging. Later, in this clinic, was introduced the use of a precipitate from the milk of thyroidectomized goats, called "rodagin." A few cases are recorded of slight improvement after continued use of this substance. Kollaritis reports no improvement in three cases in which he employed this method.

Moebius and Schultes[4] have used the serum of thyroidectomized sheep. This serum is called *antithyroidin*. Moebius reports three cases somewhat improved by this treatment and later two other cases which were benefited. Schultes and Rosenfield have likewise each reported a case. In a recent communication Moebius[5] speaks rather guardedly of the employment of this serum. Kuh,[6] after treating eleven cases with the serum, is unwilling to make any statement as to its curative effect. He thinks it relieved nervousness and diminished tachycardia.

In regard to the operative treatment, in four of our six cases the partial excision of the thyroid gland has been attended with excellent results. In two of these all the symptoms have been relieved; in one the operation was of too recent date to determine the ultimate result, but the symptoms one month after operation improved in all respects; in the other all the symptoms except exophthalmus had disappeared, and the patient is able to pursue her work. The time now intervening since operation varies from one month to four years, as shown in the table. Of the two deaths one could be ascribed to the anæsthetic, and the other, in which death took place on the eighth day with the symptoms of extreme hyperthyroidization, as a late case probably beyond possible recovery. It should be borne in mind that the operative treatment, to be of the most value, should be undertaken early, before damage has been done to the nervous system. In this condition even more than in other forms of thyroid affections, the importance of local anæsthesia cannot be too highly estimated. As further proof of the superiority of the operative treatment, the statistics of a number of observers are quoted. The best results of partial thyroidectomy yet published are those of Kocher—59 cases: 75 per cent. cured; 17 per cent. improved; 6.7 per cent. dead.

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[1] *Albany Med. Annals*, 1906, xxvii, 111.
[2] *Münch. med. Wochenschr.*, 1903, l, 146.
[3] *Deutsche med. Wochenschr.*, 1899, xxv, 627.
[4] *Münch. med. Wochenschr.*, 1901, xviii, 1873.
[5] *Münch. med. Wochenschr.*, 1903, l, 146.
[6] *Medicine*, 1905, xi, 672.

At the last German Surgical Congress, April, 1905, Friedheim from the clinic of Kümmel reported the results of twenty cases of partial thyroidectomy after five or more years had elapsed. Fourteen were cured, two much improved, three slightly improved, and one had died. In seven of the cured cases the operation had been performed nine or more years previous; in one, fifteen and a half years. He further presents the statistics of the other large German clinics for the last years as follows:

	Cases.	Cured.	Improved.	Dead.
Von Mikulicz	18	10	7	1
Krönlein	24	16	6	2
Kocher	59	45	10	4
König	8	4	..	1

SUMMARY.

In the study of this series of cases especial emphasis is directed to the following points:

I. Simple colloid hypertrophy is the most common affection of the thyroid gland. In a large percentage of cases this hypertrophy is temporary, representing, apparently, a physiological process, taking place in early adult life, and later there is a return of the gland to its normal condition. This early hypertrophy may be permanent, and in addition there may be a return of the secretory activity of the cells together with the formation of new thyroid tissue. This latter process often simulates clinically a malignant transformation.

II. Adenoma of the thyroid is by no means a rare affection. Its differentiation from simple colloid hypertrophy is readily made, both from a clinical point of view and from a macroscopic examination of the specimen. While the histologic structure of the two lesions are similar, careful examination reveals determining points of difference. The various types of adenomata, differ only from a histologic standpoint; this difference being due entirely to the secretory activity of the cells of the individual vesicles. The ademonata may occur singly or as multiple tumors of one or both lobes. Recurrence after removal is occasionally observed in tumors which from a histologic point of view, at least, are adenomata.

III. Hæmorrhage as a true etiologic factor in the production of cysts of the thyroid gland, is uncommon. By far the greatest number of cysts of the thyroid are produced by a degeneration of adenomata. The walls of these cysts we find composed of a histologic structure which exactly corresponds to one or the other of the types of adenoma. Secondary changes in the cyst walls are common, and are the result of compression and degeneration.

IV. Thyroid tumors may occur, which histologically present none of the indications of malignancy, but which clinically must be considered as such. These tumors occur outside of the thyroid gland, are probably metastatic, and usually appear in bony structures, the gland itself presenting at least no clinical evidence of primary involvement.

V. In exophthalmic goitre in addition to the type of the disease which presents a definite and constant clinical and pathological picture, there are other, so-called, irregular forms, which are associated with or occur secondarily to other thyroid affections, in which the symptom complex of Graves's disease is not complete, and the epithelial hyperplasia occurs only in foci and is of lesser degree.

VI. Tuberculosis of the thyroid, while a rare affection, is a possibility which must always be considered in diagnosis. The disease may occur in one lobe without involvement of the others, and produce a tumor which clinically simulates an adenoma, and the condition though of long standing may present no visible indications of an inflammatory condition.

VII. Carcinoma of the thyroid is more common than indicated by this series. Outside of the "goitrous districts" carcinoma occurs most often in glands that are apparently normal, and here the type of growth is that of an adeno-carcinoma.

VIII. The diagnosis of the benign thyroid affections should as a rule present little difficulty. In contradistinction to the benign lesions carcinoma does not produce a large tumor and obstructive symptoms and infiltration of the surrounding tissues occur early.

IX. The treatment of thyroid lesions with the possible exception of exophthalmic hypertrophy rests entirely upon a surgical basis. Accumulating experience likewise tends to emphasize the superiority of partial thyroidectomy over the many other methods employed in the treatment of exophthalmic hypertrophy.

X. The risks of general anæsthesia are too great to commend its employment as a routine practice in operations upon the thyroid gland. All cases can be successfully dealt with under local anæsthesia, and the primary death rate reduced thereby greatly.

PUERPERAL INFECTION: REPORT OF SIX CASES ILLUSTRATING ITS VARIED CHARACTER.*

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Puerperal infection, in spite of the increase in our knowledge of prophylaxis, is still the cause of the majority of deaths occurring in pregnancy and the puerperium, and remains, therefore, one of the most frequently discussed topics in obstetric literature. Although the pathology of the simpler or so-called "pure" forms of infection have been thoroughly described, the varied manner in which the disease may manifest itself has not been so generally understood. It seems, therefore, justifiable to add, to a subject of such perennial interest, a report of several cases studied both clinically and pathologically.

Puerperal infection differs from all other bacterial infections in that it occurs in organs whose anatomic relations and blood supply have been altered temporarily. This is of as great importance in determining the extension of the infection as is trauma in favoring the original infection. Autoinfection is to be considered also, not only as infection from organisms existing in some part of the genital canal, but also as infection which may be carried to the genitalia from some preexisting focus in a remote part of the body. Two cases of autoinfection from foci outside the genitalia are here reported. Intercurrent bacterial disease primarily nongenital must also be considered a factor in the causation of puerperal infection.

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* Published also in *American Medicine* 1906, xi, 231.

A few words concerning terminology may not be out of place, for the obstetrician is notoriously lax in his use of terms, *e. g.*, the frequent use of the term septicemia when only a toxemia exists.

In any discussion of infection we must consider on the one hand the local lesion and on the other the secondary manifestations. The local lesion is due to the toxic substance elaborated by microorganisms at the point of invasion; at the same time, these soluble substances pass into the general circulation and cause constitutional symptoms. The local lesion may be an abscess, a urethritis, or a pneumonia, etc.; in puerperal infection it is usually an endometritis. The constitutional symptoms constitute a toxemia and not a septicemia. The latter results only when the microorganisms themselves enter the blood stream and are distributed to all parts of the body. Needless to say an absolute diagnosis between toxemia and septicemia can be made during life only by the use of blood cultures. If, with the septicemia, we have the development of secondary abscesses, the condition then becomes a pyemia. Pyemic manifestations must, however, be distinctly separated from lesions of adjacent organs due to direct extension by continuity or contiguity. Thus we may have a streptococcus or other form of endometritis with toxemia or with septicemia; in the course of the latter pyemia may develop; or with either of the three conditions we may have local lesions due to direct extension of the infection. These terms include all possible forms of puerperal infection, but unfortunately, among surgeons and obstetricians the terms toxemia and septicemia do not receive their exact values.

Another stumbling block is the term sapremia, so frequently used for toxemia. Toxemia is now usually regarded as an intoxication resulting from the absorption of bacterial products. It is possible that an intoxication may be caused by substances elaborated in the bacteria-free destruction of tissue, but there is little positive evidence to this effect. By sapremia, obstetricians usually mean constitutional disturbances, as rise of temperature, pulse, etc., accompanying the retention of the products of conception. These symptoms are supposed to be due to the decomposition of the dead tissues by saprophytes with the production of the so-called "putrid endometritis." As the bacteriology of the puerperium has been more carefully studied, these cases of putrid endometritis are found to have as a basis, infection with those forms of pathogenic bacteria more difficult of isolation. This is shown by the recent investigation of Little,[1] who found *Bacillus aerogenes capsulatus* to be not infrequently present in the uterus; and also by the recent studies of gonococcus infection by Stone and myself at the New York Lying-in Hospital. It was found that the presence of the gonococcus explained a number of cases of toxemia with constitutional symptoms which would ordinarily have been classed as sapremia. It would seem advisable, therefore, to drop the old term sapremia and group these cases as toxemia from bacterial infection.

The cases* here collected illustrate some of the more unusual forms of puerperal infection both as regards the variety of causative organisms as well as the pathologic lesions.

CASE I.—*Streptococcic endometritis with septicemia; B. aerogenes capsulatus infection; acute yellow atrophy of the liver.* Records of New York Lying-in Hospital; Case No. 7,099; primipara; aged 25; pregnancy of seven months' duration.

History.—Vomiting of pregnancy was moderately severe at fourth month; but improved towards the sixth. Two days before admission the patient induced labor by passing a button hook into the uterus, rupturing the membranes. Labor pains began shortly after and the child was partially expelled on the evening of the second day. On entering the hospital the os was dilated and the child delivered. The uterus was irrigated and packed with iodoform gauze. Vomiting was incessant at entrance, and there was slight jaundice. The temperature on admission was 102°; pulse 140. On the following day the gauze was removed. Patient was restless and noisy, but rational; vomiting severe; no abdominal tenderness. Third day, slight stupor; vomiting and jaundice increased. Fourth day, profound coma; vomiting severe; vomitus stained with blood.

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*I am indebted to Drs. Lipes, Lochner and Happel for the clinical histories of the cases from the Bender Laboratory and Drs. Painter and Stone, late attending physicians to the New York Lying-in Hospital, for permission to report two cases which occurred during my service under them.

Fifth day, comatose condition continued; incessant vomiting; conjunctivas deeply bile stained and hemorrhagic. Patient died.

Urine.—Analysis showed high specific gravity, a trace of albumin, a few blood cells, granular and hyaline casts and leucin and tyrosin.

Blood cultures were negative. Blood counts showed 3,950,000 red cells, 75 per cent. hemoglobin and 18,000 to 19,500 leukocytes. The latter were divided into small lymphocytes, 75 per cent.; large lymphocytes, 65 per cent.; polymorphonuclears, 86 per cent.

*Autopsy** by Dr. Martha Wollstein. The autopsy was performed six hours after death.

Body is that of a medium-sized woman, fairly well nourished; subcutaneous fat small in amount. There is slightly marked general icterus and a group of small subcutaneous hemorrhagic spots just below and to the left of the umbilicus.

Liver.—Not decreased in size. In the mamillary line it extended to the free border of the ribs. Weight is 1,900 grams. The liver as a whole was light yellow in color and firm in consistency. On the inferior surface of the right lobe there were areas which were softer than the rest of the liver substance, and a brighter yellowish green in color. The lobules were indistinct everywhere, the central veins being plainly visible, apparently distended, but the lobules around them are not clearly outlined. In the softer areas the lobulation is almost entirely lost. Glisson's capsule is smooth and glistening, with many small hemorrhages in and beneath it. The connective tissue septums are apparently not thickened. The branches of the portal veins are, for the most part, empty. Gall-bladder contains green fluid bile; the ducts are patent. The blood in the portal veins foams, but there are no holes in the liver substance.

Spleen.—Weighs 200 grams. Crackles on pressure. Dark red in color, soft, almost diffluent, and riddled with small holes.

Stomach—Contents dark brown and fluidless. The mucous membrane is covered with blood-stained mucus and shows punctate hemorrhages, most numerous on the posterior surface.

Kidneys.—Normal in size; capsules free; cortex not thickened; markings blurred. In the boundary zone are many small hemorrhagic areas, contrasting sharply with the gray cortex and medulla.

Bladder.—Punctate hemorrhages of the mucosa near the trigone.

Uterus.—Sixteen cm. in length. Muscle is flabby and emphysematous, and peritoneal surface is normal. The endometrium is greenish black in color and gangrenous from the fundus to the lower border of the cervical lips. Attached to the mucosa at the fundus, to the left of the median line, is a mass of placental tissue which is gangrenous.

Anaerobic cultures were made from the liver, spleen and uterine wall. *Bacillus aerogenes capsulatus* grew from each of these organs.

Aerobic cultures from the liver and endometrium, gave growths of streptococci.

Diagnosis of acute yellow atrophy of liver was confirmed by histologic examination.

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*Only those portions of the autopsy protocols pertinent to the subject under discussion are given.

Pathologic Diagnosis.—Puerperal uterus; gangrenous and emphysematous endometritis; general infection with *Streptococcus pyogenes;* acute yellow atrophy of the liver; pulmonary edema; chronic pleurisy.

CASE II.—*Double pyonephrosis; pyoureter; Staphylococcus pyogenes aureus septicemia.*

Bender Laboratory Records, autopsy 0-247.

Clinical history.—Primipara. Patient was sent to the Albany Hospital for irrepressible vomiting when 8½ months pregnant. She was much emaciated and weak. Temperature was 101°-102° at night and usually subnormal in the morning. The vomiting which had persisted for two weeks was controlled by purgatives, dieting and saline enemas; but the fever persisted. The urine showed a few pus cells but no albumin. Patient was delivered at term of a dead child. Temperature went higher after delivery and the patient died on the same day.

Autopsy by Dr. George Blumer.

Left kidney.—Measures 11x5.5x4 cm. The capsule strips readily. The surface of the kidney is pale and is dotted with purulent foci which extend into the kidney substance. On section kidney tissue is exceedingly pale. Occupying the pyramid in several cases are small abscess cavities from 2 to 12 mm. in diameter. These abscess cavities are surrounded by a distinct hemorrhagic zone. In some of the pyramids near the base can be seen minute pin-point opaque areas extending into the tubules. The pelvis of the kidney contains a small quantity of purulent material and the surface is somewhat hemorrhagic. The glomeruli are visible and the cortex measures 8 mm. in thickness. In numerous areas the infection can be seen extending up along the tubules. There is marked cloudy swelling. Left ureter slightly dilated.

Right kidney.—Measures 11x6x4 cm. Capsule strips readily; surface is pale and is studded with numerous small abscesses. There is one retention cyst, 1 cm. in diameter, on the surface. On section, the tissue of the kidney is very pale and is thickly studded with small abscesses which appear to extend up along the tubules and in places show large areas of necrosis. As in the other kidney, the abscesses are surrounded by a hemorrhagic area. The cortex measures 6 mm. The pelvis of the kidney is much dilated, contains a small quantity of purulent material and its mucosa is markedly hemorrhagic.

Bladder.—Contains about 60 cc. of turbid straw colored urine; beyond some congestion, its mucous membrane is of normal appearance. The right ureter just where it passes over the pelvic brim becomes markedly dilated and at a point near the kidney measures 2.75 cm. in diameter. Throughout the dilated portion the mucous membrane is dotted with hemorrhages and in some places clots have formed. On the left side, 12 cm. above the ureteral orifice, the ureter is dilated and measures .75 cm. in diameter, while near the kidney it measures 1.75 cm. in diameter. The mucous membrane is hemorrhagic in places. Both ureters in the region of their entrance into the bladder are of normal appearance.

Uterus.—Measures 16.5x11x8 cm. There are lateral lacerations of the cervix most marked upon the right side. The fundus of the uterus contains a considerable amount of clotted blood. The interior is much roughened and the surface is exceedingly irregular. Uterine muscle is of normal appearance. The vagina is much dilated and the mucous membrane shows numerous small hemorrhages. Ovaries and tubes are normal. Placenta is normal.

Microscopic Examination.—Kidneys: The greater portion of the substance shows marked cloudy swelling. Scattered here and there through the organ, usually along the group of tubules, are areas in which the kidney substance is densely infiltrated with cells, both polynuclear and small round cells. Some of these cells are in the lumen of the tubules, others are between the tubules. Associated with these lesions is a certain amount of hemorrhage between the tubules and a considerable degree of necrosis of the kidney cells. In some places there has been an extensive breaking down of the kidney substance with the formation of abscesses. The vessels are in places plugged with bacteria.

Bacteriologic Examination.—Cultures were taken from heart's blood, liver, spleen, both kidneys, pericardium and a mesenteric gland.

Cultures from the mesenteric gland and pericardium were sterile.

Cultures from heart's blood, liver, spleen and both kidneys contained in pure culture the *Staphylococcus pyogenes aureus.*

Pathologic Diagnosis.—Infection of both kidneys with cloudy swelling. Dilation of both ureters with pyoureter. Slight pyonephrosis. Acute splenic tumor. Cloudy swelling of liver. Swelling of mesenteric glands. Slight arteriosclerosis. Persistent Meckel's diverticulum. Enlarged uterus just after labor. Infection of kidneys by *Staphylococcus pyogenes aureus,* associated with general infection of blood and organs with the same organism.

CASE III.—*Periuterine thrombophlebitis; cerebral thrombosis with purulent meningitis; pulmonary embolism; streptococcus infection; pyemia.*

Bender Laboratory Records, autopsy No. 0-554.

Clinical history.—Patient had an uneventful pregnancy until the seventh month. She then suffered from angina, which was relieved in two days by treatment with gargles and silver nitrate applications. She still suffered, however, from headache, photophobia, and restlessness; evening temperature elevated from one to two degrees.

Two weeks later, when, seven and a half months pregnant, premature labor occurred without intervention. At the termination of labor immediately after the placenta had been expelled spontaneously the patient suddenly complained of breathlessness, became cyanotic, and dyspenic, and died in less than two minutes.

Autopsy by Dr. George Blumer.

Heart.—Right side contains fluid blood and postmortem clots. Endocardium and valves are normal and the average thickness of muscle of right ventricle is 4 mm. Left side contains postmortem clots; endocardium, valves and coronary arteries are normal. Auricular appendages are empty and foramen ovale is patent but is protected by a semilunar flap. Heart muscle is pale and opaque.

Left lung.—Firmly bound down by old adhesions. It is crepitant and on section slightly edematous and congested throughout. Two of the larger pulmonary veins contain antemorten thrombi. Bronchi show slight congestion of the mucosa.

Right lung.—Slightly adherent at the apex. It is crepitant and on section the upper and middle lobes are slightly congested and edematous. The lower lobe is markedly so. Vessels in this lung appear free from clots. Bronchial glands are slightly enlarged and pigmented.

Left kidney.—Capsule strips readily, leaving a smooth surface. On section the cortex is markedly swollen and pale, the markings are indistinct and glomeruli are scarcely visible. Veins contain fresh thrombi and a fresh thrombus is present in the main branch of the renal vein.

Uterus.—Measures 14x10x5.5 cm. The musculature is flabby, averaging 1.5 cm. in thickness and endometrium is rough; a mass of adherent material with the appearance of blood clot, is in the fundus over an area 5 cm. in diameter. The peritoneal surface is smooth. The tubes and ovaries are normal. Vaginal tissue about the cervix is cyanotic and shows a few hemorrhages. Veins in the broad ligament contain red and mixed thrombi, which are more numerous on the left side.

Brain.—Shows, on the surface, three distinct areas of softening. The largest is on the right side at the vertex in the region of the first frontal convolution, the second is on the right side in the region of the upper part of the parietal lobule and the third is on the left side, just anterior to the fissure of Rolando, involving the ascending frontal convolution.

In connection with all these areas beneath the pia-arachnoid there are collections of yellowish green pus. The longitudinal sinus contains parietal antemortem clots; the lateral sinus is free from clots.

Bacteriologic Examination.— Coverslips from the uterus show cocci in chains, not decolorizing by Gram, and bacilli decolorizing by Gram.

Cultures from spleen, bile, and meninges were sterile. Cultures from uterus and left renal thrombus show *Streptococcus pyogenes* and *Proteus vulgaris.*

Pathologic Diagnosis.—Thrombosis of veins of left broad ligament and left renal veins. Thrombosis of branches of the right pulmonary veins. Thrombosis of the longitudinal sinus. Multiple thromboses of cerebral vessels with areas of softening. Purulent meningitis over these areas. Chronic adhesive pleurisy on left side. Cloudy swelling of heart muscle, liver, and kidney. Acute splenic tumor. Puerperal uterus.

CASE IV.—*Suppurative salpingitis and perisalpingitis; lymphangitis; septic endometritis; general suppurative peritonitis from infection with the streptococcus, the gonococcus and the colon bacillus; septicemia.*

Record of New York Lying-In Hospital, Case No. 8410.

Clinical history.—Primipara, aged 18.

Previous history.—Six days before entering the hospital labor pains set in and the patient was delivered of a seven months' child by an outside physician. The child lived one hour. Bowels moved with an enema on the second day and at this time there was "fever" and abdominal pain. On the sixth day she was sent to the hospital, having suffered with pain in the lower abdomen and "fever" during this time.

Condition at entrance on sixth day postpartum.—Pulse 110, high tension, regular. Temperature 104°, no abdominal tenderness. No rigidity.

Uterus seems well involuted. Vaginal examination shows many condylomas and profuse purulent discharge. The uterus is anteverted, soft, tender and fixed. Os admits one finger, no placental masses are felt. On palpation in the lateral fornixes, extreme tenderness is elicited. Left appendage seems negative; but on the right there is a moderate sized fixed mass. No mass or swelling is found in the cul-de-sac. Rectal examination corroborates vaginal.

Smear taken from inside of the cervix shows gonococci and streptococci. Culture from the uterus showed streptococci in pure culture. Blood culture on the sixth day was negative. Leukocyte count was 29,000, of which 90.5 per cent, were polymorphonuclears. Urine showed a trace of albumin with hyaline casts. Leucin and tyrosin were absent. The diagnosis at this time was septic endometritis with gonorrheal salpingitis.

On the seventh and eighth days her condition was unchanged. Bowels moved freely. Evening temperature was 102° with morning remission. There was slight pain in the hypogastrium. On the eighth day temperature was 103° in the evening and pulse 100. No abdominal rigidity was shown.

On the ninth day, after a large bowel movement patient complained of sudden and severe abdominal pain and difficulty in breathing. Pain was referred to the epigastrium and right lumbar region. It was peristaltic in character, intermittent, and intense. The tongue was dry and there was slight vomiting of clear green fluid. Pulse rose to 120, was thready and of high tension. Abdomen was very markedly rigid and tender. Expression was anxious and patient cried out with pain.

Vaginal examination showed slight fullness in the cul-de-sac with marked tenderness, otherwise as before. Leukocytosis at this time was 11,000, of which 89.2 per cent were polymorphonuclears.

Patient was put on the operating table four and a half hours after onset of acute pain and rigidity. Laparotomy was done under ether anesthesia in Trendelenberg position with median incision.

On opening the peritoneum large quantities of seropurulent fluid escaped. Severe general peritonitis was present with marked congestion of the visceral blood-vessels. Peritonitis was most intense in the pelvic region. Appendix was adherent to right tube and ovary. Right tube was large, much thickened and inflamed and covered with tags of adhesions. Pus exuded from the fimbriated end. There were the remains of many recent adhesions in the region of the right tube and in the right side of the pelvis. Right tube and ovary were removed with the uterus, leaving the left tube and ovary and stump of cervix. The entire peritoneal cavity was flushed with hot saline solution. Iodoform gauze drain was passed through the cervix and abdomen closed by through-and-through silkwormgut sutures, as patient's condition was poor. Death occurred after four hours without rally.

Blood taken from vein just before operation and placed on serum agar and ascitic agar yielded no growth.

Cultures taken at operation from the peritoneal pus, and from the fimbriated end of the tube showed *B. coli* and streptococci; from the inner end of the tube, no growth; from the uterine cavity, no growth.

CASE V.—*Acute suppurative (postabortive) endometritis salpingitis; acute fibrino-purulent peritonitis; general infection with pneumococcus; pyemia.*

Records of the Bender Laboratory, autopsy 0-756.

Clinical history.—Patient, aged 20. Para II, four months pregnant. Abortion was induced by a midwife by means of a catheter. Infection resulted. She was admitted to the Albany Hospital and the uterus was curetted and packed; but she died three days afterwards. Temperature was 102° at admission and ran from 102° to 103° until death from peritonitis.

Autopsy by Dr. Stanton.

Abdominal cavity.—All peritoneal surfaces are covered with a sticky, grayish yellow, purulent exudate which is thin between adherent surfaces of peritoneum, but reaches 1 mm. to 4 mm. in thickness over the peritoneal surfaces held apart by collections of fluid. Omentum completely covers intestines, its free border reaching down into the pelvis, where it is covered with a thick layer of fibrinopurulent exudate. The pelvis and dependent portions of the abdomen are filled with a yellowish turbid fibrinopurulent exudate. The subperitoneal bloodvessels are everywhere deeply injected. The urinary bladder is distended, reaching 3 cm. above the pubes. Appendix measures 8.5 cm. in length, has a free mesoappendix, extends downward and inward over the brim of the pelvis and is negative, except for exudate on the peritoneal surface.

Uterus and appendages: These are covered with a black layer of fibrinopurulent exudate. The fimbriated extremity of the left tube is turned upward, is deeply congested and exudes a thick creamy pus when the tube is compressed. Right tube extends downward, backward and outward, the fimbriated extremity lying behind and below the ovary, and is embedded in a thick layer of the fibrinopurulent exudate. Both tubes are deeply congested, somewhat swollen and on pressure a thick cream colored pus can be forced from both abdominal and uterine ends. Mucosa of the tubes is deep red in color and is covered with cream colored pus; ovaries are deeply injected and covered with a fibrinopurulent exudate.

Uterus: This is enlarged, globular in shape, extending upward to the level of the promontory of the sacrum, is distinctly retroflexed. Cervix measures 2.5 cm. in diameter and projects 1 cm. into the vagina. Cervical canal is dilated, easily admits one finger and measures 3 cm. in length; external os is deeply congested and covered with a yellow purulent material. Uterine cavity above the internal os measures 7.5 cm. in length; the muscle is firm; the inner surface of the uterus presents a grayish granular surface with areas of bluish black and deep red discoloration. There is no evidence of endometrium.

Vagina: Negative except for congestion and bluish discoloration in the region of the cervix. This is especially marked in the posterior fornix.

Right common iliac vein contains several grayish granular masses 3 mm. to 5 mm. in diameter, the remains of softened thrombus.

Bacteriologic Examination.—Smears from the peritoneum show numerous cocci in pairs and short chains with numerous bacilli of varying morphology.

Cultures from peritoneum, liver, spleen and kidney show numerous minute translucent slightly raised colonies on agar from which are obtained lanceolate diplococci staining by Gram's method. Subcultures from these minute colonies were sterile after 48 hours. On original cultures were also moist, semitranslucent colonies 1 mm. to 3 mm. in diameter, from subcultures of which was obtained a gas-producing bacillus which coagulated milk with acid reaction.

Cultures from the uterus showed a large number of organisms which were not worked out.

Microscopic Description.—Uterus: Mucosa has been removed. Muscular walls show narrow zones of necrosis adjacent to uterine cavity. Small bloodvessels near cavity are thrombosed. Considerable leukocytic infiltration of all tissues with scattered masses of bacteria.

Tube is markedly congested and lumen is filled with pus. Serous surface is covered with an exudate of fibrin and leukocytes. All coats are infiltrated with polynuclear leukocytes and lymphocytes. Fibroblasts with a few new formed bloodvessels are found beneath the exudate on the peritoneal surface. Gram-Weigert stains show numerous cocci in pairs and short chains, and long rod-shaped bacilli.

Pathologic Diagnosis.—Acute suppurative salpingitis and endometritis. Acute fibrinopurulent peritonitis. Mural thrombus of right heart. Congestion and edema of the lung with hemorrhages. Slight cloudy swelling of liver and kidneys.

CASE VI.—*Acute hemorrhagic endometritis; acute suppurative peritonitis and pericarditis; septic pneumonia with pleuritis; Staphylococcus pyogenes aureus infection; pyemia.*

Bender Laboratory Records, autopsy 0-198.

Clinical history: After an apparently normal pregnancy, patient was delivered by a midwife and entered the hospital on the eighth day postpartum very profoundly infected. Death occurred 36 hours after, her condition being so bad that nothing could be attempted in the way of operative measures.

Autopsy by Dr. George Blumer.

Peritoneal cavity contains about 300 cc. of turbid purulent fluid. Both layers are dull, injected and covered with a small amount of fibrin. Intestinal coils and omentum are adherent to one another by fresh adhesions. Appendix is normal. Retrosternal glands are not enlarged.

Pericardial cavity: Distended with 250 cc. of turbid yellow fluid. Both layers are dull and slightly injected.

Left pleural cavity: Contains about 1,000 cc. of turbid serous fluid. Right pleural cavity also contains turbid fluid.

Left lung: Pleura is covered by layers of fibrin and lymph. Both lobes are crepitant and on section are congested and edematous. Bronchi are congested and covered with mucopurulent fluid. Bloodvessels are normal.

Right lung: Bound down by fresh adhesions on all its surfaces. Pleura is also covered by layers of fibrin and lymph. Lung is less crepitant than normal and lower lobe feels quite solid. On section lower lobe shows bronchopneumonic areas and elsewhere lung is congested and edematous.

Uterus is enlarged, subinvoluted, soft and measures 12 x 8 x 5 cm. Peritoneal covering is injected and covered with a plastic fibrinous exudate. The os is patulous and escaping from it is a large amount of sticky blood-stained material. The endometrium is markedly congested and shows a few discrete submucous hemorrhages, the mucosa is covered with tenacious foul mucoid fluid. Uterine walls are 2 cm. in thickness. Mucous membrane of the vagina is congested and shows a few hemorrhagic points. Tubes and ovaries are apparently normal.

Bacteriologic Examination.—Smears from fluid of pleura, pericardium and peritoneum contain many polymorphonuclear leukocytes with round cocci, generally single, which do not decolorize by Gram's method.

Cultures from spleen and gallbladder are negative. *Staphylococcus pyogenes aureus* is obtained in pure culture from liver, pleura and uterine cavity. Cultures from the bronchopneumonic areas of lung and from peritoneum show colon bacillus as well as *Staphylococcus pyogenes aureus.* Kidneys give a pure culture of colon bacillus.

Pathologic Diagnosis.—General infection with *Staphylococcus pyogenes aureus.* Infection of kidney, lung and peritoneum with *B. coli communis.* Bronchopneumonia with edema of the lungs. Acute bronchitis. Fibrinopurulent peritonitis, pericarditis and pleurisy. Acute splenic tumor. Cloudy swelling of kidney. Subinvoluted uterus with acute hemorrhagic endometritis.

DISCUSSION OF CASES.

CASE I.—Legg's statistics show that 69 of 100 cases of acute yellow atrophy occurred in females and in 25 there was the association of pregnancy. Thierfelder collected 143 cases, of which 88 occurred in females and in 33 instances it was associated with pregnancy. However, acute yellow atrophy is also found in association with many other conditions and with bacterial infections. Among the bacterial diseases may be mentioned typhoid fever, diphtheria, erysipelas, osteomyelitis and puerperal infection. Richter[2] has collected 41 cases of acute yellow atrophy in association with syphilis. Babes[3] has reported 5 cases following streptococcus infection and Ballin[4] has collected 10 cases following chloroform anesthesia.

Hyperemesis gravidarum is a not infrequent association with acute yellow atrophy. Stone[5] reports one case of acute yellow atrophy with this association and collects a large number of others. Meyer-Wirz[6] among other degenerative changes in the liver of patients dying from eclampsia found one case of acute yellow atrophy, not associated with puerperal infection.

The frequent occurrence of infection in association with eclamptic and other toxemias of pregnancy is well known. Schrieber[7] in a statistical study, reports that out of 29 deaths with eclampsia 7 died of sepsis, and Meyer-Wirz,[8] in 117 cases of eclampsia, had 35 deaths, in which puerperal infection had supervened in three and in an additional case there was septic pneumonia. However, the toxic symptoms, as shown by the vomiting, were not severe in the case reported here; but it seems that the association of infection and pregnancy is a factor of some significance in the production of acute yellow atrophy of the liver. Strictly speaking, this should, perhaps, be considered a complication of pregnancy rather than an example of puerperal infection. In view, however, of the probability of the infection beginning in the genitalia it may justly be considered here.

CASE II.—Pyonephrosis is a rather uncommon complication of pregnancy, but hydronephrosis and dilation of the ureters does not appear to be so. Olshausen[9] has reported 16 cases of dilation of the ureter, in 12 of which the condition was unilateral and in 10 of these on the right side. This distribution is supposed to be due to the greater frequency with which the fetal head lies in the right oblique diameter of the pelvis. In this case the position was l. o. a., but the measurements of the pelvis were not noted. It may be possible that a generally contracted pelvis with an obliterated promontory would permit pressure to come upon both ureters at the pelvic brim and cause such dilation of the ureters as occurred in this case.

Cragin[10] in a study of 10 cases of pyelitis complicating pregnancy, states that according to Vinay[11] this condition depends upon two etiologic factors: (1) Pressure of the ureter by the pregnant uterus; (2) infection of the urinary tract above the point of compression. Cragin states that in his cases the clinical course was marked by right-sided pain, sometimes elicited only by palpation or sudden motion. A rise of temperature usually occurred. He states that irritability of the bladder with frequent micturition is common, but that "the infection is a descending one and cystitis, when it does occur, is usually secondary to the pyelitis and ureteritis."

The experiments of Rebdaud and Bonneau upon animals are quoted in support of this view. These investigators produced pyonephrosis by aseptic ligation of the ureter and the injection into a distant part of the body of streptococci or colon bacilli.

The case reported, because of the exemption of the bladder and the lower part of the ureter, seems to have been a descending infection. Staphylococcus infection in such cases is rare; colon infection is by far the most frequent cause according to the collected cases of Cragin. One instance of streptococcus infection has been reported by Vinay and one of gonococcus by Loy.

It is interesting to note in view of the recently advanced theory of the common origin of eclamptic toxemia and toxemia of pregnancy with vomiting that this case was admitted to the hospital for pernicious vomiting and that Meyer-Wirz in his 35 autopsies for eclampsia noted bilateral hydronephrosis and dilation of the ureters in one case.

Rochard[12] reports a case of severe bilateral pyelonephritis in advanced pregnancy with immediate recovery after delivery of twins. He quotes Kendirdjy's statistics of 62 cases among which there were only two deaths, and advises expectant medical treatment, but states that if interference is necessary premature delivery should be the rule rather than an operation on the kidney. Cova[13] has reported 21 cases in which nephrectomy was done with resulting abortion in only five. The danger of involvement of the second kidney is so great that it would seem preferable to remove the cause of compression of the ureter rather than to remove the kidney.

Fournier[14] has reported two cases of this condition with varied course. In one there was gradual onset in the early months of pregnancy, premature labor and birth of a dead child at seven months. In the other there was an acute attack, nephrotomy and labor at term. Schwab[15] also reports two cases, in one there was a history of gonorrhea and the infection was severe, but patient went to term. The second case was one of hydramnios and ran an apyretic course. The colon bacillus was the infecting organism and a live child was born at 8 months of pregnancy. Schwab draws attention to the difficulty of diagnosis and of the difficulty of differentiating from appendicitis.

Cathala[16] in a clinical and pathologic study of pyelonephritis in pregnancy states that there are two main causes: (1) Predisposing cause, the lessened resistance of the pregnant woman to bacterial infection and the retention of urine from compression with its associated congestion. (2) Determining cause, the penetration of the infecting organism to the kidney. He divides the clinical course into two periods: that of onset, in which there are symptoms of general infection; and that of attack, in which there are symptoms of chronic suppurative pyelonephritis. He concludes that the prognosis for the child is bad, for if pregnancy does go to term, the infant not infrequently is of small size and weak.

CASE III.—Periuterine thrombophlebitis is a most serious condition and is the most frequent predisposing cause of pulmonary embolism and sudden death in pregnancy. Grossman in a study of 51 autopsies upon puerperal women dying from infection found periuterine thrombophlebitis alone in 14 instances and associated with lymphangitis in 13 other instances. Other veins in addition to the hypogastric and ovarian were involved in all cases save one; in three instances the vena cava was also included.

Richter[17] lays stress upon Mahler's sign (" Kletter symptom "), the rapid beat of the heart due to extra work and slight degeneration. He has collected results from 16,000 cases and found 78 cases of thrombosis and 20 cases of embolism; of the last 60 per cent were fatal. Mahler's sign was found in 98 per cent of these cases.

The thrombosis may be due to mechanical causes, but is more frequently associated with infection. The initial lesion in the case reported here would appear to be the infectious process in the throat. This case is possibly, therefore, one of autoinfection, as is the case of pyonephrosis.

CASE IV.—Gonorrheal infection in the puerperium has been much discussed among obstetricians and widely divergent opinions are held in regard to its incidence and its influence upon tissues altered by pregnancy.

Kronig's[18] study of 179 cases of puerperal fever showed that *M. gonorrhoeae* was found in 50 cases, while Williams[19] found the organism in 8 of 150 cases of puerperal fever. Vogel[20] in 24 cases of puerperal fever found gonococci 4 times, twice in pure culture and twice in association with streptococci. Foulerton and Bonney[21] examined 54 cases with negative results. Stone[22] and myself, in a study of 53 selected cases of pregnancy, found the gonococcus in 17. In three cases labor was premature.

Martin[23] kept under observation 13 cases of chronic gonorrhea during labor and the puerperium and in none of these were symptoms observed which could be attributed directly to the venereal disease. There were no abortions, although in one case labor was hastened by an acute exacerbation of the disease. In four cases the puerperium was practically normal and in the remainder there was a rise of temperature coming on rather late. This the author considers characteristic of the disease.

Lea,[24] taking acute purulent conjunctivitis in the infant as a proof of gonorrheal infection of the mother, has collected 50 cases. In 60 per cent there was an uneventful puerperium, while 40 per cent. had more or less acute inflammation of the pelvic organs. Acute purulent endometritis with pyrexia as the most common condition, while in 10 per cent acute pelvic peritonitis existed. All the patients recovered save 3, who were also infected with the streptococcus. In institutions, however, acute purulent conjunctivitis in the child is not a just criterion of the frequency of gonorrheal infection of the mother, for Holt[25] has noted the frequent transmission of gonococcus infection among infants that are segregated in hospitals.

The presence of a mixed infection of the gonococcus and some other organism is said to add greatly to the severity of the infection and many cases have been reported to sustain this view. However, the severity of the constitutional symptoms seems to depend more upon the extent of the anatomic lesion than upon the character of the infection.

Case V.—Pneumococcic puerperal infection is an extremely rare condition and is usually an infection from without. Weichselbaum,[26] as well as Bar and Tissier,[27] have met this condition, and Cohn has described a case very similar to the one here reported. His patient after abortion developed a pneumococcic endometritis and later a fatal meningitis. Foulerton and Bonney[21] also report a similar postabortive infection from pneumococcus with five other cases of pneumococcus infection following full term pregnancies. They conclude that the grade of infection is, as a rule, not severe and that their series of cases cannot be taken as a just indication of the frequency of this form of infection.

Case VI.—General septicemia is not an infrequent termination of puerperal infection. The clinical course is usually that of a rapidly progressive acute infection and follows the same course as other septicemias not of puerperal origin. Streptococcus infection is the most frequent and severe type of infection after labor. If the number of cases studied by Czerniewski, Kronig, Williams, Vogel and Foulerton and Bonney be collected, it is found that of 498 cases in which the contents of the uterus was examined bacteriologically, streptococci were present in 200 (40 per cent). While streptococcus is so frequent, *Staphylococcus pyogenes* *aureus* is most infrequent. Foulerton and Bonney found this organism but once in 54 cases and it is but infrequently mentioned by other writers. *Staphylococcus pyogenes aureus* was found in two of the six cases in this study; in one the infection was of the kidney and in the other an acute general infection of all the organs.

CONCLUSIONS.

A consideration of these six cases teaches many things in regard to the diagnosis and management of puerperal infection in the more advanced stages of the disease. It may be seen that while streptococcus infection is usually the most common and severe type of infection, other organisms which usually produce clinically mild symptoms, may run a severe course and cause death.

Autoinfection must be considered to include infection from foci of bacterial disease in distinct parts of the body. Pregnant women suffering from such distant infection require most watchful care. Autoinfection from the genital canal is probably more common than is generally supposed. This is indicated in a study by Bumm and Sigwart[28] of the bacteriology of the secretions of women in the later months of pregnancy. The streptococcus was found to be present in more than 38 per cent. of the cases and they conclude that with very careful examination aerobic streptococci may be found in the secretions of at least 75 per cent of all women during pregnancy and the puerperium. Of the women having streptococci, 20.4 per cent had fever.

From this fact it may be seen that the presence of pathogenic microorganisms in the genital canal is by no means sufficient evidence upon which to base a diagnosis of puerperal infection, and even when combined with constitutional disturbances the first step only has been taken toward the proper diagnosis of the condition. The term puerperal infection should be broadened to include infection elsewhere than in the uterus, and the location and nature of such lesions should be recognized before any operative measures are undertaken. This can only be done by exact physical examination, examination of urine, blood, etc., and a proper knowledge of the varied anatomic manifestations of infection. The frequency with which pain is right-sided in hydronephrosis and pyelitis should be remembered in differentiating the diagnosis from appendicitis.

The utter futility, and even harmfulness, of curettement, if attempted in such cases as those here reported, is readily seen; and when the varied character and oftentimes widespread distribution of puerperal infection are considered, the explanation for the high mortality (over 70 per cent) of hysterectomy in that condition is obvious.

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A NOTE ON EMBRYONIC GLANDULAR TUMORS OF THE KIDNEY WITH THE REPORT OF A CASE.

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In 1899 Birsch-Hirschfeld, in a study of the tumors of the kidney, classified as embryonic glandular tumors those new growths which formerly had been termed adenomyoma, adenosarcoma and adenomyosarcoma, names which were descriptive of the tissues of the tumor but which did not indicate their origin. He proved that these tumors had a common origin in embryonic life.

Such tumors are not of infrequent occurrence, forming as they do twenty-eight per cent. in Walker's collection. They occur nearly always in children; only two cases have been reported in adults, that of Hoisholt in a male of eighteen years and that of Muus in a female of thirty-four years. Their growth is rapid and they metastasize early and after removal generally recur *in situ*. In spite of their malignant nature this form of tumor has attracted very little attention in this country, for from 1899 until the present time I have found only one reported case, that of Blumer in 1903.

All these tumors have in common a glandular tissue and an embryonic or archiblastic tissue which resembles closely that of sarcoma. In addition to these tissues smooth and striated muscle, cartilage, fat and connective tissue are commonly present. They grow almost without exception in the pelvis or medulla of the kidney and extend outward toward the cortex, gradually compressing the kidney tissue until it forms a capsule for the tumor. Metastases develop generally by way of the blood vessels and but rarely by way of the lymphatics. The various tissues of the primary growth are reproduced. The minute structure of these tumors varies within wide limits, owing to the variable proportion of the tissues present.

The case here reported occurred in the practice of Dr. Charles S. Jennings of Detroit, Mich.; no clinical notes or autopsy report could be obtained.

The exact dimensions of the kidney cannot be determined because the specimen has been sectioned and portions removed. The tumor is nearly globular, located within the substance of the kidney and measures 3.5 cm. in diameter. The surface is fairly smooth with here and there furrows marking definite lobulations; the consistence is firm. It is partially surrounded by kidney substance which forms a capsule 0.6 cm. in thickness and where the kidney tissue ends the fibrous capsule continues over the tumor.

On section the tumor is solid and of fibrous structure. Definite masses of fibres arranged in large bundles pass in various directions and give to the tumor an appearance identical with that of a myoma of the uterus.

Attached to the kidney at the hilum is a considerable amount of fibrous tissue in thin layers suggesting that it may have formed the wall of a large cyst the contents of which have been lost. In this tissue are some smaller cysts containing a colloid-like material and numerous large blood sinues. The exact relationship of the cysts to the kidney cannot be made out because the specimen has been so badly torn.

The microscopic appearance of the parenchyma of the kidney is normal; there is, however, on the outer surface of the capsule an exudate of fibrin and polymorphonuclear leucocytes indicating a perinephritic infection.

The tumor has no distinct capsule separating it from the kidney substance and in places it invades the kidney. The growth at no point extends beyond the capsule of the kidney. Its finer structure presents a much more complicated picture than the gross appearance indicates. Several varieties of tissue are to be considered, as follows:

A.—Glandular tissue in the form of tubules running in all directions, appearing in longitudinal and cross section. These tubules are apparently of two kinds—those belonging to the kidney which have been enclosed in the peripheral parts of the tumor, and those which form an integral part of the growth. This second form of tubule originates in the youngest portions of the growth from accumulations of small round deeply staining cells situated in and derived from the archiblastic tissue. The glandular elements are small in amount and form only a small part of the tumor.

B.—Embryonic or archiblastic tissue forms a considerable portion of the tumor and represents that portion which is growing most rapidly. In appearance it closely resembles sarcomatous tissue; the cells are large, round or oval, with pale staining nuclei and are packed closely together with no stroma. It is in this tissue that the groups of small round cells are found from which the tubules are developed. Blood spaces are very numerous in some parts of this tissue so that it resembles angio-sarcoma closely. At the hilum this tissue forms long cylindrical projections which rapidly undergo degenerative changes. In the more advanced of these the archiblastic tissue is replaced by what appears to be fibrous connective tissue often mucoid in character. The connective tissue at the periphery rapidly undergoes hyaline degeneration so that finally the cylinder consists of a central axis of mucoid connective tissue surrounded by a mass of homogeneous hyaline-like material. Blood vessels are very numerous in these projections, while glandular elements are relatively scarce. Several dilated, almost cystic, spaces were found in the cylinders lined by flattened epithelium which suggests that probably the cysts mentioned in the gross description were formed in this way from the tubules.

In the absence of any autopsy record the presence of metastases was not determined.

In reconstructing the tumor from the individual tissues that have been described we find that the smooth muscle represents the oldest portion and is located in the substance of the kidney growing into it and enclosing tubules and glomeruli. For this reason tubules and glomeruli are found in the myomatous portion of the tumor.

The archiblastic and glandular tissue represent the youngest and most rapidly growing portion of the tumor and is always found at a distance from the kidney. It extends into the fibrous tissue at the hilum in the form of cylinders as described above. The cartilage fat and connective tissues are very scanty in amount and are found near the archiblastic tissue.

From this description it is clear that this tumor began its growth within the kidney, probably near the hilum, that it is of congenital origin and that it must be classed as a mixed tumor, belonging to the group classified by Birsch-Hirschfeld as embryonic glandular tumors.

The method of development of these tumors has been the subject of much controversy and several theories have been advanced which for the convenience of description may be divided into two groups.

A.— The development of the tumor from cells within the kidney. The older view that these tumors should be classed as primary carcinomata or sarcomata of the kidney is no longer considered correct. A carcinoma develops from fully developed epithelial cells in an adult organ, whereas these tumors are found almost exclusively in very young children and metastasize by way of the blood vessels. To be classed as sarcoma it must be assumed that the glandular tissue has sprung from kidney tubules, which is not the case, as has been seen in the tumor just described. The tubules are an integral part of the tumor and take an active part in its growth.

The more recent view that these mixed tumors have their origin in tissues present in the kidney of the embryo is supported by Busse and Muus. The former found, in a fœtal kidney, tissues which closely resemble those occurring in these tumors and he is convinced that the tumors take their origin from such tissues.

Muus believes that a portion of the embryonic kidney takes on a pathological growth and so forms a tumor. The various tissues of the tumor are supposed to originate by metaplasia from the tissues of the embryonic kidney, thus sarcoma-like tissue from round cells, epithelium from the interstitial tissue, mucoid tissue, cartilage and fat from connective tissue, smooth muscle from that normally present in the kidney, striated muscle from smooth muscle.

B.—The theory that the tumors originate from embryonic cells outside the kidney but enclosed during development. This view is strongly supported and was originally advanced by Birsch-Hirschfeld, who believes that a portion of the Wolffian body in the embryo in some way becomes enclosed in the developing kidney and forms the starting point of the tumor. Vogler, Merkel, Heincke, Sander and Blaess also accept this view. Wilms calls attention to the fact that the Wolffian body contains no striated muscle and that none is present in any of the organs developing from it. The metastases furthermore contain all the varieties of tissue found in the main tumor, so that a metastasis of cells representing all these tissues is unlikely. He concludes from this that the origin of the tumors must be placed at a much earlier period of embryonic development when the cells are undifferentiated, that is, germinal tissue cells which in their later development are capable of forming all these various tissues.

These cells might be misplaced at the time when the primitive segment and lateral plates are formed from the middle germinal layer. The striated muscle develops from the myotom of the primitive segment from which all the striated muscles of this region develop. The smooth muscle, fat, connective tissue and cartilage originate from the scleratom of the lateral plates while the epithelium originates from the nephrotom (Wolffian body).

If a small portion of these structures become misplaced and take on a pathological growth it would readily explain the various tissues found in these tumors.

The presence of cysts in association with these tumors has not been mentioned so far as can be found in the literature. The formation of the cysts in the tumor here described seems to have taken place either by hæmorrhage and degeneration in the archiblastic tissue or in a gradual dilatation of the tubules. This view lends support to the theory already generally accepted that cysts of embryonic origin result from misplaced mesodermal tissue.

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TUBERCULOSIS OF AN ADENOMYOMA OF THE UTERUS.*

By J. L. ARCHAMBAULT, M. D.

WITH A PATHOLOGIC REPORT

By RICHARD M. PEARCE, M. D.

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That tumors in general are not subject to invasion by bacteria, other than those of the pyogenic group, is well known. The simultaneous occurrence of carcinoma and tuberculosis in an organ or tissue is occasionally reported, but the invasion of other tumors by the tubercle bacillus is very unusual. This is especially true of uterine myomata which are seldom involved in even the most extensive tuberculous infections of the adjacent mucosa. The case here reported is of interest not merely on account of the rarity of the condition, but also because of the absence of tuberculosis in the mucosa of the general uterine cavity with but a slight lesion in one tube. The tuberculosis of the myoma and that of the tube were secondary to tuberculosis of the lung, but apparently independent of one another and due to infection through the blood stream. As a fairly exhaustive review of the literature fails to reveal an analogous condition our observation appears to be worthy of record. A detailed report follows:

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Clinical History.—H. E., aged 20, an only child, unmarried, was admitted to the Cohoes Hospital, January 10, 1906. Her family history offers several points worthy of note. Her mother presents evidence of tabes and her father died at forty-six of a valvular lesion of the heart which formed part of the plainly luetic condition. Her grandfather, on the mother's side, had syphilis, and the grandmother succumbed to general paralysis. There is no direct tuberculous heredity.

Personal History.—The patient had measles in early childhood and showed some indications of hereditary syphilis, viz.: A slowly-healing ulcer of right leg and a nose of the saddle type.

Menstruation beginning at sixteen, has always been very scanty, irregular and tardy, with occasional amenorrhea for periods of five to six months. An epistaxis, apparently vicarious, had been frequent. Menstruation, at first painless, later became more difficult. At no time had there been leucorrhea. Dec. 14, 1904, a pelvic examination showed the uterus to be very small, of the infantile type, and lying in a moderate degree of retrodeviation, with some tenderness in the region of the left ovary.

July 30, 1904, the patient had a sudden attack of hemoptysis. A careful physical examination gave evidence of a localized adhesive pleuritis of the left apex, overlying an area of tuberculosis, involving a considerable part of the apex and extending down and outward toward the axillary line. After a sojourn at the seashore and in the mountains she was considerably improved in general health, while the physical signs had manifestly retroceded and in part entirely disappeared. The following winter (1904) was passed in the mountains and she returned in April still more improved. July 15, 1905, she had a second very slight hemoptysis, but improved rapidly, gaining by November 13, twenty-nine pounds.

Present Illness.—Abruptly, about November 21, she began to complain of soreness and pain in the hypogastric region. The pain was dull in character, intermittent, returning especially in the latter part of the day, and exaggerated by fatigue and standing. The patient had not menstruated in five months. As the pain continued unabated for a week, without any appearance of the menstrual flow, she was advised to return home. On bimanual examination, the cervix was found deviated toward the pubes and the Douglas cul-de-sac occupied by the enlarged fundus of the retroverted uterus. The fundus gave the sensation of a firm mass of about the size of a mandarin and somewhat irregular in shape, being larger on the left, and very slightly movable. The left lateral cul-de-sac was also occupied by another swelling less firm and less voluminous, having neither the fibromatous woody feeling of the main tumor nor the fluctuation of a cyst; this second enlargement seemed almost contiguous with the uterine body. The condition of the right adnexa could not be defined. These conditions were not present at the previous examination, eleven months before.

At this stage, the pulmonary condition presented a marked change. While no advancement of the disease was evident in the left apex and the corresponding axillary region, two new foci had appeared; one in the left base posteriorly and the other in the right interscapular space, close to the spinal column.

December 15, menstruation occurred and lasted five days. After a few days interruption, there was again some slight bloody discharge. This discharge kept on thereafter, more or less irregularly, until the time of operation. The pains became gradually more intense, finally requiring the daily use of some sedative for their control.

January 5, the size of the pelvic mass was considered to have increased materially. On that same date, a few tubercle bacilli with a great number of diplococci and streptococci were found in the sputum. Three previous examinations of the sputum had been negative.

Much concern was naurally entertained as to the exact nature of the uterine condition. The first diagnosis was simply one of a solid tumor, probably a fibromyoma, occupying the posterior wall of the uterus. A closer study, however, of all the evidence suggested the possibility of a tuberculous lesion of the uterus, and this possibility was carefully explained to the family.

Of course, on account of their rare occurrence, the diagnosis of any of the pelvic forms of tuberculosis is seldom made until the abdomen is opened, and even then not infrequently only after the specimen is in the hands of the pathologist. Uterine tuberculosis has no well-defined symptomatology. In the present instance, if a probable diagnosis of a tuberculous condition of the uterine growth was arrived at before operation, it is willingly conceded that we expected to find as well a similar condition of the adnexa and of the peritoneum; that is, a general abdominal tuberculosis. In holding this view, we were influenced by the existing pulmonary condition and by abdominal symptoms which predominated especially during the very last weeks. When the abdomen was opened, it was a surprise, therefore, to find that, aside from numerous and extensive adhesions of an inflammatory nature, the general as well as the pelvic peritoneum was free from tuberculosis.

Surgical Report.—January 11, laparotomy; medium incision nine centimeters long. A coil of small intestine was found drawn down into the pelvis and firmly adherent close to the right uterine cornu, evidently accounting for the pain in the abdomen which had been so striking a feature. Both ovaries were fibrocystic. The uterine body, enlarged to the size of an orange, lay deeply in Douglas' cul-de-sac and was so matted up in adhesions that a subtotal hysterectomy was performed. The appendix was inspected and, being healthy, was left undisturbed.

Convalescence was uneventful, and the patient reported April 16, that she had gained ten pounds in weight and was in the best of health.

PATHOLOGIC REPORT BY DR. RICHARD M. PEARCE.

Gross Description.—The specimen consists of a uterus with its appendages. The former is exceedingly firm and almost globular in shape, measuring 17.5 cm. in circumference just below the level of the attachment of the Fallopian tubes and 19.5 cm. over fundus and cervix. The cervix protrudes beyond the globular body as a short, thin, circular process, 0.8 cm. long and with walls 0.4 cm. thick. Its edges are smooth, rounded and grayish-white in color. The peritoneal surfaces are covered more or less uniformly by coarse fibrous adhesions. On section the entire length of the uterus from cervix to fundus is 6.8 cm., the greatest thickness, antero-posteriorly, 5 cm. The body itself is 6 cm. in length. The anterior wall is normal in appearance, though slightly thickened, and measures 1.4 cm. at the mid portion of the uterine cavity. The fundus is 1.7 cm. in thickness. The posterior wall is occupied by a globular mass extending from the median line of the fundus to the internal orifice of the cervix (5.2 cm.) and laterally from the peritoneum to the uterine cavity (4 cm.). This mass is composed of firm, dense, grayish-white tissue having a whorl-like appearance and resembling the structure of myoma in a general way, but riddled everywhere by cavities varying from those miliary in size to those 0.5 cm. in diameter. From these cavities escapes a thick, yellow, more or less tenacious pus. The walls of the larger cavities, after the escape of the fluid pus, are seen to be lined by a yellow, soft granular material, suggestive of caseation. These areas extend to within two millimeters of the peritoneal surface and toward the median line approach and apparently involve the mucosa. The cervix is not involved. The uterine canal is 4.7 cm. long, 1.2 cm. of which is cervical. It is greatly narrowed and 2 cm. below the fundus is almost entirely obliterated. In or beneath the mucosa covering the lower portion of the tumor are numerous closely-set, fine, yellowish miliary areas. These do not involve the mucosa of the anterior wall nor that of the cervix.

The tubes and areas are atrophied. The left tube and ovary are bound to the uterus by fibrous adhesions; the right is free and has a smooth peritoneal covering. Each ovary contains a few small cysts.

Bacteriology.—Cover glass preparations of material from the cavities in the tumor, stained by methylene blue, show pus cells which take the stain well, many poorly-staining necrotic cells, and much granular detritus but no micro-organisms. Attempts to demonstrate the tubercle bacillus and the gonococcus are negative.

Agar, blood serum and hydrocele-agar tubes are sterile after 72 hours.

HISTOLOGIC DESCRIPTION.

Sections Passing Through Uterine Wall and Tumor.—The greater portion of such show a diffuse tuberculous process in a tissue composed of smooth muscle fibers and containing widely scattered tubular glands. The uterine wall proper, measured beneath the cover glass, is 3 mm. in thickness. No tubercles are present in the slightly thickened peritoneal covering, but between it and the musculature small tubercles are occasionally seen. In the muscle itself, which contains an increase of connective tissue, are a few well-developed tubercles with caseous centers. About the blood vessels are numerous lymphoid cells. The line between the normal uterine musculature and the tumor in the upper portion of the uterus is intact, but in the submucosa are irregular accumulations of lymphoid cells. At a point where the definite arrangement of the musculature ceases there is an abrupt transition to diffuse tuberculous tissue containing numerous giant cells and characterized by extensive caseation; few typical tubercles can be seen. In the midst of this are found here and there isolated areas of smooth muscle, containing tubular glands. These latter are lined for the most part by several layers of cylindrical cells, of the type found in the uterine glands, but are tortuous and show more or less irregular dilations. They are not infrequently arranged in clusters and have branching prolongations with but a single layer of epithelium. In the masses of muscle a moderate amount of connective tissue is present and also a slight infiltration of lymphoid cells. The glands are found throughout the new tissue, even at a distance of 2 cm. from the uterine wall and have no relation to those of the mucosa. There is no evidence that the channel of the tuberculosis infection was along these glands.

Sections taken at three levels and passing through entire wall of apparently normal portions of uterus opposite tumor show no evidence of tuberculosis. The mucosa in each is normal. A section through the cervix shows no lesions.

A section across the entire uterine canal at a point of greatest constriction shows partial obliteration, but no tuberculosis of the mucosa. The lumen at this point contains a small plug composed of mucus, leucocytes and desquamated epithelial cells.

Right Fallopian Tube.—The mucosa is entirely destroyed. The surface is a chronic granulation tissue with, in its deeper layers, more or less newly formed fibrous tissue. Epithelioid cells are not abundant and are very diffusely arranged. But one definite tubercle with typical giant cell is seen. An occasional oval fibrous and hyaline area is suggestive of healed tubercle, as are also a few small foci of lime salts. In the deeper layers of the muscle coat are accumulations of lymphoid cells and old blood pigment, but no tubercles.

The left Fallopian tube is atrophied, but otherwise not noteworthy. The ovaries are fibrous and contain a few small cysts, but show no evidence of tuberculosis.

Careful examination of the peritoneal surfaces of the uterus, tubes and ovaries fails to reveal lesions of tuberculosis.

PATHOLOGIC DIAGNOSIS.

Tuberculosis of an adenomyoma of the uterus. Tuberculosis of right Fallopian tube. Atrophy of ovaries and Fallopian tubes. Chronic perimetritis and perisalpingitis.

REMARKS.

As already stated, we have made a search, although not exhaustive, of the medical literature for analogous cases, but have failed to find such.

Closely resembling the case here reported, however, is one observed at the gynecologic clinic of Zurich by C. Bole (du Locle).[1] A summary of this case reads as follows:

History.—Woman, aged 50; heredo-tuberculosis; menstruation at thirteen; leucorrhea. Patient married twice, no children. Dysmenorrhea and loss of strength.

Present State.—Uterus anteflexed, movable, slightly tender on pressure and about the size of a child's head in volume.

Diagnosis.—Uterine myoma.

Laparotomy.—Total hysterectomy after Freund's method. The tumor, when extirpated, is twice as large as one's fist. The macroscopic and microscopic examination showed that it was a rare case of myoma associated with an ascending uterotubal tuberculosis. The vaginal mucosa was not involved, and the etiology could not be determined.

This case, however, is not identical with the one here reported. The tumor is intramural, but the tuberculosis is spoken of as an ascending uterotubal infection, and the myoma as associated with it. From this it may be inferred that the mucosa alone was involved in the tuberculous process. This inference also finds support in the statement that the histologic researches bore only on "the superficial portions, in a state of necrosis." Thus it would appear from these comparisons that our case might indeed, deserve to be considered as unique.

Kelly[2] states that "tuberculosis of the endometrium is exceedingly rare as complication in the large myomatous uterus." He has met but one case, and in this the disease had extended into both tubes.

A last point not to be overlooked is the mode of infection or of transmission to the uterine parenchyma.

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[1] Genækologia Helvetica, 1903, p. 99.

[2] "Operative Gynecology," vol. ii, p. 381.

As regards the pathogenesis of the local lesions in our case, it seems very plausible that the adenomyoma constituted the primary lesion and that the tuberculous infection occurred secondarily. But how did this infection take place? How in this particular case was it transmitted from the lungs?

From the clinical history and from the findings at the time of the operation it seems fair to believe that the propagation of the lesions to the uterine tissue took place through the blood current, and in a similar manner, to the only tube involved.

Infection by means of the blood stream seems to be well supported by the conclusions of M. Schakoff,[3] which may be given as follows:

Genital tuberculosis in women is generally secondary to a florid or latent tuberculosis of the lungs or of the peribronchial lymph nodes, less frequently to an intestinal tuberculosis. The genital tuberculosis is generally propagated by the blood stream, except in the case of vaginal tuberculosis, which may proceed from inoculation by contact.

Tuberculous peritonitis occurs frequently during the evolution of a genital tuberculosis, especially after a tuberculous salpingitis. Any portion of the genital tract may be affected; the tube is involved more frequently, the vagina less often. These inoculations take place by the blood stream; therefrom the uterus or the ovary may become infected by contiguity. Generally the uterus is infected by descending contagion; it may, however, be involved in the first place. A pre-existing disease and the puerperal state may act as predisposing causes. The uterine cervix is rarely the seat of tuberculosis. The tuberculosis of the ovary is almost always consecutive to a tuberculosis of the Fallopian tube, of the peritoneum, or of the rectum; the propagation occurs by contiguity or by way of adhesions. Independent foci may, however, be found in the ovary without any lesions of the surrounding structures; in such cases these foci have been set up by the blood stream.

In the above conclusions, the two points of practical bearing on our case are: 1. Genital tuberculosis in women is generally secondary to pulmonary tuberculosis. 2. In tuberculosis of the uterus or of the ovary, when the tuberculous lesions are found as independent foci without lesions of the surrounding structures, the inoculation has taken place by the blood current. That the latter would appear to be the case is indicated by the absence of tuberculosis in the mucosa, not only of the uterine cavity generally, but also in that covering the tumor itself. It is possible that alterations in the blood supply of the tumor caused a condition of degeneration or necrosis constituting a *locus minoris resistentiæ* and a point of selection for tubercle bacilli reaching these areas through the blood stream.

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[3] "Contributions to the Knowledge of Tuberculosis of the Female Genital Organs," Gynäk. Helvet., 1904. p. 139.

A REPORT OF FOUR INSTANCES IN WHICH GIANT CELLS OCCURRED IN UNUSUAL SITUATIONS,

With a Brief Review of the Literature of Giant-Cell Formation.

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The object of this communication is to report four instances in which giant cells occurred in unusual situations and to bring together in this connection some of the more important literature relating to giant-cell formation.

Accordingly to the circumstances under which giant cells are found, we are accustomed to recognize three main groups: the myeloid type occurring in normal bone marrow and in sarcoma, the Langhans giant cell, characteristic of tuberculosis, and the foreign body giant cell. Upon morphological grounds, however, the latter two groups might be brought on account of the mural arrangement, in most cases, of their nuclei, into a single group, as distinct from the myeloid type, in which the nuclei are distributed irregularly throughout the cell. While finally, if function is considered, it is evident that all may be brought in a single group: that of cells having a destructive action more or less analogous to that of phagocytic cells. This function of the myeloid giant cells of the bone marrow, also known as "myeloplaxes" (Ziegler) and osteoclasts is well recognized, as it is also of the general group of multinucleated cells found about a great variety of foreign particles and the remains of tissue destruction. Concerning the Langhans type, although the evidence is not so clear, there is much to indicate that they may have a similar function.

Despite the fact that much has been written concerning the origin and nature of giant cells, there is little uniformity of opinion. The type of giant cells which has aroused the greatest interest and discussion, in this regard, are those occurring in the lesions due to the tubercle bacillus.

In regard to the formation of these cells, we have two principal views: that of the French school, led by Metchnikoff, and that of the German school, consisting of Weigert and his adherents, among whom are, Baumgarten, Marchand and Klebs. Both schools hold that the giant cells develop from large formative cells, but there is a difference of opinion as to the nature of the cells. Metchnikoff claims that they are of leucocytic parentage, while Weigert thinks they spring from connective tissue or endothelial cells. Again their method of development gives rise to differing views. Some authorities hold that the individual cells, from which the giant cells develop, group themselves around masses of bacilli and become fused, without division of their nuclei. Opposed to this is the view of Weigert, who thinks that they are formed by amitotic or direct division of a single nucleus and cell. Metchnikoff states that giant cells thus formed have ameboid movements and are phagocytic, in that they digest and otherwise remove the tubercle bacilli. On the other hand we have positive assertions that the multinucleated masses possess neither ameboid nor phagocytic qualities. The difficulty does not end here, for different views are also held in regard to the nature of the cellular cytoplasm. Weigert and his associates insist that the central cytoplasm is in the process of necrosis, the nuclei being placed in the more vital parts of the cell. Metchnikoff thinks that the centre of the cell, although appearing necrotic, is especially active, the nuclei being grouped in the less active parts. In other words it is Metchnikoff's opinion that the giant cells of tuberculosis are living and defensive cellular masses, while Weigert is convinced that they are the seat of a progressive necrosis and are without function.

Koch is one of the few Germans whose views do not differ in every respect from those of Metchnikoff. He regards the giant cells as being permanent structures possessed of more vitality than the bacilli which they contain; he says he has seen many cells containing degenerated forms of bacilli, which he contends have been destroyed by the cellular protoplasm. He thinks that the tubercle bacillus on its entrance into the organism is first attacked by the "microphages" or polymorphonuclear leucocytes; these are later joined by the "macrophages" which develop into epithelioid cells and which in turn form giant cells. In experimental tuberculosis he found giant cells containing bacilli, which from their staining characteristics and morphology, were evidently degenerated forms; this degeneration being due to changes brought about by the cells containing them. Miller is also convinced that the included bacilli undergo degeneration, for the reason that he has seen many of them colored black with osmic acid. Shüppel and Ziegler found various concentric, lamellated, calcareous, concretions in the interior of tubercle giant cells. These formations Metchnikoff regards as the result of the calcification of the tubercle bacillus in the interior of the cells, and a step in the process of the reaction of the giant cell against the contained bacillus.

Stschastny and Welcker also found degenerated forms of the tubercle bacillus in giant cells in experimental tuberculosis of the rabbit and guinea pig. Unna disagrees with Metchnikoff's view, that degeneration of the included bacilli is an indication of the phagocytic power of the enveloping cell. He attributes this degeneration to the poisonous agent which has paralyzed the affected parts of the cell, and not to any activity of the giant cell itself.

Weigert, in direct opposition to Metchnikoff, Stschastny and Welcker, says that the forms, which the latter claim to be degenerated bacillary bodies, are merely artefacts, or else particles of a granular material having no relation whatever to the tubercle bacillus.

It is apparent that the question of the origin and nature of the tubercle giant cell is no nearer a satisfactory solution than it was when Langhans first suggested the theories of progressive nuclear division of cellular confluence. It seems, however, to be generally agreed that the cells, which either by confluence of the protoplasm or by nuclear division, give rise to the multinucleated masses, are those to which the name epithelioid has been given.

Before the discovery of the tubercle bacilli by Koch it was held by many, that the giant cell of tubercle owed its origin to metamorphosed blood vessels, but of late years this view has been practically abandoned for lack of supporters. In tuberculosis of the liver, Klebs thinks that many of the giant cells there found, are formed from the lining epithelium of the biliary ducts. A somewhat similiar view is held by Arnold, who in miliary tuberculosis of the kidney and liver, found giant cells which were formed apparently by the confluence of neighboring epithelial cells lining detached portions of urinary tubules and bile ducts.

In connection with the giant cells of tuberculosis, Hektoen's studies have added greatly to our knowledge of the fate of these masses. He concludes that in the healing of non-degenerated tuberculosis tissue, the multinucleated giant cells may either disintegrate and subsequently become absorbed, or may divide again into smaller cells. The latter occurs more frequently. Under certain conditions after thus separating into smaller cells they may undergo progressive changes. This leads him to doubt the theory of Weigert and others that giant cells are necrobiotic elements doomed to destruction, and to support the teleological view held by Metchnikoff, that they are defensive plasmodia, in that they engulf and destroy the tubercle bacillus.

Unna in his work on the histopathology of skin lesions discusses at considerable length the nature of the giant cells found in lupus. He believes that the bacilli within the giant cells elaborate a poison which paralyzes certain parts of the cell. In the neighborhood of the nuclei this poisonous action is not only resisted, presumably as a result of nuclear influence, but the nuclei proliferate and elaborate an antitoxic substance which neutralizes the action of the bacterial poison. While nuclear proliferation lasts, he concludes, there can never be complete necrosis of the giant cell.

Concerning the foreign body giant cells which may readily be studied experimentally a large mass of literature is at hand. As their function appears to be to remove dead and useless fragments of tissue, or to surround and render innocuous particles of extraneous matter which have found their way into the tissue, they are seen under a great variety of conditions. The substances most frequently enclosed by them are bits of hair, degenerated or cornified epithelium, cholesterin and fatty acid crystals, old pigment of the blood, extraneous insoluble particles, sutures, etc. To quote a few specific examples of but one type, suffice it to state that LeCount has described cholesterin giant cells in an old hydrocele, Meyer in foreign body peritonitis, Manasse in polypoid growths of the middle ear, Cramer and Schultz in a tumor of the eye and Ruge and Kruchman in sebaceous cysts.

One of the most interesting studies of foreign body giant cells is the experimental investigation of Faber. He introduced agar into the subcutaneous tissues of rabbits and observed the changes which followed. After various intervals he found about the particles of agar, leucocytes, epithelioid cells and giant cells. He found that the latter not only surrounded the small masses of agar but also sent processes into their substance. In some of his experiments he used agar impregnated with Berlin blue, and thus was able to obtain positive evidence that digestion was really taking place within the multinucleated cells, for it was easy to demonstrate that in such cells, in addition to the larger masses of foreign material, were many fine colored particles which had been broken off from the former in the process of its digestion. Indeed he saw some cells which contained only particles of Berlin blue and no large agar clumps.

Other experimental investigations have yielded similar results. Among the substances used in the experimental studies are small particles of sterile sponge, catgut, bits of glass, pollen grains, lycopodium spores and coagulated blood serum.

There are almost as many theories concerning the origin of these foreign body giant cells as there are writers dealing with the subject. Many authorities have reached the conclusion that the cells which take up foreign bodies are proliferating fixed tissue cells. Langhans in 1868 in his elaborate discussion of the subject originated the first theories as to giant cell formation, and, although somewhat modified, these still hold to-day. He suggests two possibilities: (1) that they may arise from a single cell by multiplication of the nucleus, or, (2) they may result from the fusion of many cells into one. To the former Dürck has given the name "proliferation giant cell" and to the latter "conglutination giant cell." Ziegler says that if the formation of giant cells is associated with an inflammatory reaction and if the proliferating tissue contains leucoctyes, the latter may develop into giant cells by a division of their nuclei and act as phagocytes. Several German writers hold that it occasionally happens that mononuclear cells take up small foreign bodies into their substance and through continued nuclear division become converted into giant cells. Virchow concluded that foreign body giant cells were altered lymph vessels. Koster thought they came from the endothelium of blood vessels. Of late years, however, investigators have been in general accord in denying the vascular origin of the multinucleated cells, although one or two recent writers have brought forward the theory again. Weiss, who made a thorough study of this subject, concluded that the giant cells which he found surrounding foreign bodies were always formed by the confluence of the protoplasm of neighboring cells, the latter being in most cases "granulation cells." Faber, as the result of his experimental subcutaneous introductions of agar, is positive that the giant cells which he noted were formed by the merging together of numerous epitheloid cells. Goldman regards the multinucleated cells which form around hairs in a dermoid cyst as arising from a single polymorphonuclear leucocyte by the division of its nucleus. On the other hand Buxton says that the leucocytes of the early invasion do not give origin to foreign body giant cells for several reasons: (1) because the latter are not seen until granulation tissue has begun to form, (2) their formation begins at that point of the foreign body which is nearest to the granulation area, and (3) in general their appearance both as regards nucleus and protoplasm closely resembles that of epithelioid cells. Marchand concludes that the cells in question are formed from epithelioid cells, which in turn develop from the endothelium of capillary blood vessels, thus indirectly returning to the views of Virchow and Köster that they arise from blood vessels.

Observation No. 1.—Multinucleated cells within the bronchi in bronchiectasis.

(Records of the Pathological Department, University of Pennsylvania, No. 01.46.) Autopsy by Dr. Pearce. Clinical Diagnosis:*—Pulmonary tuberculosis and pneumonia.

Anatomical Diagnosis.—Chronic interstitial pneumonia (diffuse); acute lobar pneumonia (right upper lobe); bronchiectasis, emphysema; general arteriosclerosis; chronic mitral and aortic endocarditis; hypertrophy of left ventricle; general chronic passive congestion; congenital hypoplasia of right kidney; compensatory hypertrophy of left kidney; chronic fibrous peritonitis; chronic fibrous pleuritis.

Lungs.—The lungs are smaller than normal and very firm. Posterior surfaces are covered by adhesions. On section there is seen a very definite diffuse increase of connective tissue. Throughout both lungs, but more especially in the lower lobes, are many closely set, minute cavities, apparently dilated bronchi, containing a thick mucus which is adherent to their walls. About these the new formation of connective tissue is very evident and often takes the form of grayish tubercle-like masses. There is a well marked dilatation of the air vessels throughout the lungs, especially along the anterior edges, where small blebs 2 to 3 mm. in diameter may be seen. The right upper lobe is prominent, of a grayish red color and completely solidified. On section it is grayish red in color, finely granular, and on pressure a large amount of yellowish-gray fluid escapes. In the midst of this solidification is a dilated bronchus 1.5 cm. in diameter. The bronchi contain a large amount of grayish yellow, and in some places, slightly greenish mucus disagreeable in odor.

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*For the autopsy notes from which this abstract of gross findings is taken I am indebted to Prof. Allen J. Smith, of the University of Pennsylvania.

Histological Examination.—Throughout all portions of the lung the air cells are largely obliterated and replaced by a very dense and very vascular connective tissue containing many lymphoid and plasma cells. In this tissue is a moderate deposition of carbon pigment. Special stains show it to be unusually rich in elastic fibres. The air cells which remain are enlarged. The bronchi, with the exception of the larger structures are for the most part greatly dilated and present very irregular outlines. In short the condition present is a chronic interstitial pneumonia with emphysema and extreme bronchiectasis, and, as the chief interest lies in the giant cells within the bronchi, the latter structures only will be described in detail.

Of the smaller bronchi a few are of normal diameter and some are collapsed, but for the most part they are greatly dilated. Their walls are greatly thickened and the mucosa irregular and convoluted. Into some the newly formed connective tissue has sent finger-like projections, these causing more or less invagination of the mucosa. The epithelium of the smaller bronchi is not infrequently separated from the underlying structures and thrown into reduplicated folds. The cells of these smaller tubes are of the low columnar type and stain deeply with hematoxlyin. Not infrequently they penetrate in an irregular manner the surrounding tissue. All the bronchi with the exception of the very largest are partially filled with masses composed mainly of a thick hyaline mucus, with, in addition, polymorphonuclear leucocytes, epithelial cells and cellular detritus and a few red cells. The mucus which holds the mass together has in places a more or less fibrillated appearance, suggesting a fibrin network; elsewhere it is homogeneous. In the center or at the periphery of many of these masses are seen one or more large multinucleated cellular masses which vary considerably in appearance. In outline some are almost spherical, while others are very irregular or elongated. The irregularity is never so great as to suggest the presence of cell processes similar to those of the tubercle giant cell. The nuclei range in number from 2 to 80 or 100 and are oval and vesicular; the nuclear chromatin appears very plainly and takes a blue stain with hematoxylin, while the protoplasm stains a light pink with eosin. Many of the cells are vacuolated and the vacuoles contain in many instances a poorly staining granular material, the nature of which cannot be determined.

The nature and mode of formation of these multinucleated cells cannot readily be determined. A careful review of the literature reveals no mention of similar cells under like circumstances. They are not a manifestation of the lesions of tuberculosis or syphilis, and it cannot be shown conclusively that they are foreign body giant cells which have formed about mucus or detritus in the bronchi, though the occasional occurrence of crystal-like fragments within their protoplasm suggests such a possibility. As this possibility, however, presupposes the conglutination of proliferation of desquamated epithelial cells it is hardly worthy of consideration. It is, however, evident that they must in some way have been formed from the epithelium of the bronchi. Careful study of many preparations has shown that not infrequently small masses of the cells forming the epithelial lining protrude in sprout-like processes into the lumen. These cells lose more or less their cylindrical form and constitute an irregular arrangement of nuclei without distinct cell outlines. It is possible that these cell masses could become constricted at their bases and finally separate entirely from the mucosa and by contraction form round or oval multinucleated cells resembling giant cells, which in the fluid of the bronchi might retain for some time their normal staining characteristics. Such a mode of origin, however, cannot be demonstrated.

The possibility that these cells are but the tips of budding processes separated by the knife from the cell strands connecting them with the underlying mucosa, and therefore analogous to the multinucleated masses seen in the placenta, has been considered. A study of serial sections, however, has shown this not to be the case.

That giant cells commonly arise from epithelial cells is doubtful, but that they may do so is evident from a number of investigations. In tuberculosis of the intestine, Gaule thought that some, at least, of the giant cells originated in the epithelial lining of the tubules. Similarly Klebs and Arnold, as stated above, in tuberculosis of the liver and kidney, thought that the existing giant cells were formed from the lining epithelium of the bile ducts and the uriniferous tubules. Pearce in his study of experimental cirrhosis of the liver, found multinucleated masses, essentially foreign body giant cells, since they were active in removing necrotic hyaline liver cells. These he declares are derived in part from endothelial cells and in part from liver cells. C. Friedländer, in a peculiar form of pneumonia to which he has given the name "Desquamative Hepatization," describes giant cells in the alveolar spaces, which he thinks originate from the lining of the alveola.

The occurrence of cells so typically of the giant cell type in such a place is so unusual that one hesitates to offer an explanation. It seems justifiable, however, in view of the fact that origin from either desquamated epithelium or the cells emigrating from the blood stream appears untenable, to conclude that they must be pinched off masses of excessively proliferating sprouts of the bronchial epithelium, which still retain more or less their natural staining characteristics.

Observation No. II.—Giant cells in a Carcinoma of the Tongue. *(Records of the Bender Laboratory, Surgical Path, No. 06-535.)*

The tumor was one involving the right half of the tongue, right tonsil and adjacent lymph nodes. It presented, except for extensive necrosis, the usual gross appearance and histologically was of little interest except for the presence of large numbers of multinucleated cells in and about necrotic epithelial pearls containing much kerato-hyalin. These cells lay in dense masses of lymphoid and plasma cells and in intimate contact with fragments of keratinized epithelial cells and oftentimes formed a perfect ring about smaller disorganized epithelial pearls. They had in some instances a round or oval outline, but the majority were very irregular, a considerable number sending elongated processes of their protoplasm into the surrounding tissue.

In the protoplasm many vacuoles are seen, some being free of all contents while others contain a variable amount of hematoxylin staining material. Not infrequently the material within the cells can be definitely recognized as fragments of degenerated epithelial cells. The vesicular nuclei, some of which are round, others oval, are situated as a rule at the periphery or at the poles, though an irregular arrangement is not uncommon. The larger cells contain 40 to 50 nuclei. There is no evidence of nitosis.

Concerning the occurrence of giant cells in epithelial tumors there is very little to be said.

In several cases of nævo-carcinoma, Unna describes giant cells, similar to those of tuberculosis in that their nuclei are peripherally placed. Malherbes and Chenantais saw similar cells in epithelioma of the sebaceous glands of the neck. Krauss in 70 cases of epithelioma found giant cells in 10. He also found them in an epithelioma of the clitoris and in several adenomata. In an epithelioma in which calcification had taken place, Denecke also saw such cells. Krüchman observed them in carcinomata of the eyelid and of the œsophagus. Becher found multinucleated cells in several cases of lipoma and carcinoma of the upper and lower lips. Delamare and Lècene, out of a total of 250 epitheliomas examined, saw giant cells in 14, the majority being found in squamous cell carcinoma of the tongue, cheeks, larynx, œsophagus, tonsil, gums and çervix. Cramer and Schultz noticed similar cells in a pseudoglioma of the retina.

In some cases, as in the one here reported, the giant cells are scattered throughout the area of round cell infiltration and in close proximity to the masses of cornified epithelial cells or so-called "pearls." This association has suggested the possibility that they represent an attempt to remove the new growth and bring about a spontaneous healing. This question has been answered affirmatively and negatively by both French and German writers. That giant cells can surround and remove vigorously growing cells is very doubtful, but that they may take a part in removing cornified epithelium or other inert material, as they do elsewhere in the body, is very probable. Becher even goes further than this and says that it is the function of the giant cell to bring about organization of the "epithelial pearls" and their spontaneous healing, making it possible for them to be replaced by connective tissue. Unna thinks that the presence of giant cells in carcinoma suggest some infectious agent as the causal factor. In this connection it may be recalled that Unna describes multinucleated cells in various of the more uncommon skin lesions. He found in Spiradenitis disseminata suppurativa, a diffuse inflammation of the sudoriparous glands, that the epithelial cells of the ducts become swollen, separate and sometimes form multinucleated masses which he thinks are typical giant cells. Although unable after examination to find any specific micro-organisms, nevertheless, from the nature of the lesion, he thought that the condition pointed to an inflammation of infectious origin.

Mibelli, in acne keloid, found giant cells around the hair follicles. This led Unna to consider that this disease also was caused by a distinct infectious agent the nature of which is unknown. In varicella, Unna also describes giant cells in the prickle cell layer of the epidermis, and on account of their peculiar form gave them the name "balloon" giant cells.

Observation No. III.—Giant Cells in a Recurrent Granulation Polyp of the Aural Canal. *(Bender Laboratory Records, Surgical Path. No. 06-332.)*

The gross appearance of the tumor, a small polyp, is of no special importance. Microscopically, it is in part necrotic with extensive leucocytic infiltration and in part composed of a matrix of newly-formed connective tissue with a small round cell infiltration. Here and there a slight amount of œdema is noticeable. Scattered throughout the latter tissue are a number of protoplasmic masses irregular in outline with no definite limiting wall and containing 3 to 15 oval, vesicular nuclei. The nuclei are arranged irregularly throughout the cells, in some, crowded together in the center, in others, at the poles or periphery. Many of these cells contain a granular material staining with hematoxylin and resembling epithelial debris.

The occurrence of giant cells in aural polyps has been reported several times. Krüchman describes one and Manasse nine cases of granulation polyp of the middle ear in which giant cells were found. Manasse decided that they are of foreign body origin and have nothing to do with the formation of the polyps as such. Since giant cells are very often found in chronically inflamed tissue we have no new condition here. They indicate probably the presence of foreign particles used in medication, or possibly desquamated epithelial cells or fragments of adherent cerumen.

Observation No. IV.—Giant Cells in the Wall of a Cyst of the Broad Ligament. *(Records of the Bender Laboratory, Surgical Path. No. 05-1304.)*

Macroscopically the specimen may be described as a cyst measuring 12 x 8 x 7 cm. with areas of subcapsular hemorrhage. The walls are quite thick and firm in consistence and the contents a dark brown mucoid fluid in which are mingled brownish friable masses. In several places the wall of the cyst is irregularly thickened and contains minute cysts.

Microscopic Description.—Sections through the cyst wall show two zones. The outer consists of old fibrous connective tissue with a large number of small blood vessels. The inner is composed of young granulation tissue with its new blood vessels and small accumulations of leucocytes. Scattered profusely throughout this granulation tissue are small, round, oval or irregularly shaped hyaline masses, many of which are surrounded by multinucleated masses of protoplasm. These latter are of various shapes and sizes corresponding to the enclosed material. The nuclei are of the oval vesicular variety, the larger cells containing from 50 to 100. These nuclei are also varied as to their situation, some being massed in the center, a few at the periphery, while others are arranged at one or either pole. The enclosed material is apparently of a mucoid nature, which it would appear has become adherent to the granulating surface and surrounded in the process of repair, with the ultimate formation of giant cells about the less soluble particles.

It is interesting to note that in 1870 Langhans noticed somewhat similar phenomena about extravastated blood or blood introduced as a coagulum into the cutaneous tissues of various animals. In each instance the fluid portion of the blood was soon absorbed. Around the remains of the clot he saw multinucleated giant cells and was positive in asserting that absorption was due to the phagocytic action of the latter.

A few cases of giant cells found in connection with cyst formations have been reported by German writers. Goldman and F. König describe multincleated cells in the walls of dermoid and atheromatous cysts, Bohm in a traumatic epithelial cyst, and Kühne in a cyst of the œsophagus.

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SPONTANEOUS AMPUTATION OF AN APPENDIX VERMIFORMIS CONTAINED IN A FEMORAL HERNIA SAC.

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Within the past few years and especially since the time when the radical cure for hernia became customary, a large number of cases of hernia have been reported in which the appendix alone or accompanied by omentum, or omentum and intestine have been found occupying the sac. Previously, only isolated cases appear in the literature. Probably the first reported was that of Morgagni in 1751. Piersol, in 1901, collected 125 reported cases, and since that time a number of communications have appeared in rapid succession, describing instances of appendices found in the various hernial sacs, the greater majority being found in right-sided herniae, especially the inguinal form. Edington, Bidwell, Eccles, Keetley and Southan have described cases in which the appendix was the sole occupant of the sac.

Most of the cases have been found at operation, while a few have been accidentally found at autopsy. It is now known that the appendix is present in about one or two per cent. of all hernias.

Hernia of the appendix may be either congenital or acquired. According to Hutchinson all the congenital cases are right sided and of the inguinal form. In the acquired forms the usual causes of hernia, as general enteroptosis together with the unusual mobility of the appendix are the main etiological factors. It is more common in children and advanced life than in early adult and middle age. According to Rivet's figures seventy per cent. occurred in men and thirty per cent. in women. The inguinal form constitutes seventy to eighty per cent. of all cases; the femoral twenty to thirty. Of the fifty-three cases of strangulated appendix in a hernia sac recently collected by Clogg three only occurred in males, and of these three, two were infants. Both were inguinal hernias—fifty occurred in women and in each instance the hernia was femoral.

Pathological conditions of the herniated appendix, especially those of an inflammatory nature, are not uncommon. "The tendency to inflammation of the appendix is greater than in the unherniated organ" (Jopson) and irreducibility, according to Bararde's statistics, is almost the rule. In his ninety-seven cases inflammation was found in thirty and strangulation in forty-seven. In many instances the symptoms supposed to be due to a strangulation of the hernia have been found to be due to an inflamed or gangrenous appendix, which had become adherent to a hernial sac. Eccles states that the inflammation of the appendix in these cases takes place after its prolapse into the hernial sac, and that the strangulation is secondary, being caused by an acute inflammatory process taking place in a confined space.

Kleberg describes a most interesting case in which the appendix was found in a left-sided hernial sac at operation. After having made the incision he noticed a gangrenous piece of tissue which later sloughed off, and was described by the pathologist as appendiceal tissue. Shaw and Stanton describe a case of hernia of the appendix in which the appendix was found to be intimately attached to the epididymus. Wölfer and McArthur each report a case of cystic appendix in the sac of a hernia and Wood has called attention to the danger of rupture by taxis when a cystic appendix is in an inguinal hernia. Such an accident is reported by Van Hook. Various other interesting conditions of the inherniated appendix are possible, but all may be summed up by stating that conditions which may affect the appendix when in its normal position may affect the appendix also when within a hernia sac. We can find, however, no reference in the literature to the spontaneous amputation of an inherniated appendix and for this reason feel justified in placing on record such a case although the condition must be considered more as a curiosity than as one of clinical or pathological importance.

Case Report.—Mrs. M. E. G., aged 80, housewife, entered the Albany City Hospital, service of Dr. A. W. Elting on March 9, 1906. The family history is negative.

Past History.—The patient first noticed a small lump in the right groin about eight years ago. This swelling gradually increased in size until it reached the size of a goose egg and was recognized as a hernia. At first it gave rise to no symptoms, but later, on the entrance of a portion of the intestine into the sac, the patient would have a feeling of weight and suffer extreme pain. She was able at such times to reduce the hernia and would then be relieved. She has worn a truss for the past three years. The rupture "comes down" about every six or eight months.

Present Illness.—The patient felt perfectly well until she was taken with slight pain in the right groin, which increased in severity until it was so severe as to be intolerable. She did not vomit. The bowels were constipated and the hernia irreducible.

Operation.—With the patient in dorsal recumbent posture there presented a sausage-shaped tumor, well down in groin on the right side, which measures about 8.5 x 3.5 cm. An effort was made at reduction while on the table, but without avail. An incision was made over the tumor mass parallel with Poupart's ligament and the tissues separated and the hernia sac exposed. The sac was opened and found to contain three to four inches of ileum markedly congested and almost black. The neck of the sac was very tight, being of the size of a finger, and it was necessary to incise the constricting band somewhat. Some hot saline solution was poured on the gut and the color began to return with contraction of muscular fibres. The gut, after considerable effort, slipped back into the abdomen. What was considered as a properitoneal lipoma was attached to the inner surface of sac. On close examination of this mass was found what appeared to be a rather short obliterated appendix with smooth ends and without caecal attachment, which had apparently been amputated by pressure. To this was attached a definite mesentery. A considerable tongue of omentum was deligated along the sac. The patient made an uninterrupted recovery.

Gross Description of Specimen.—Attached to an apparently smooth serous membrane (hernia sac) measuring 3.5 cm. in diameter is an irregular mass of adipose tissue closely resembling that of the meso-appendix. Attached to this mass and slightly imbedded in it is a cord-like structure which measures 4 cm. in length and 0.5 cm. in diameter. Its surface is smooth, glistening, pinkish gray in color and it is rounded off at both ends. To these ends are attached by fibrous bands small masses of adipose tissue. Adherent to the hernia sac at its under surface by a long fibrous band is a piece of omentum containing considerable fat. *Anatomical Diagnosis.*—Hernia sac containing omentum and a portion of an appendix (spontaneous amputation).

Histological examination of the appendix shows the lumen to have been entirely obliterated and the mucosa completely replaced by fat and connective tissue containing a few lymphoid cells. The musculature is slightly atrophic, and there is a light infiltration of lymphocytes and eosinophiles. The peritoneal coat here and there shows many small hemorrhages. That the structure is appendix and not some other obliterated tubular structure or ligamentous mass is definitely determined by the character and arrangement of its outer coats. *Microscopic Diagnosis.*—Chronic obliterative appendicitis.

The only problem of pathological interest in this condition is the question of the sequence of the obliteration and amputation. It seems most probable that the obliteration of the appendix had occurred before the organ entered the sac, though of course it is not possible to exclude a gradual obliterative appendicitis occurring after its entrance. Under either circumstance it would appear to be quite certain that the amputation was due to the gradual constriction of the proximal portion of the appendix between the divisions of the fascia lata forming the boundaries of the femoral opening, this force being aided in part perhaps by the pressure of the truss. That the constriction leading to amputation as primary, or due to an acute inflammatory condition causing adhesions about the proximal portion of the appendix, appears very improbable, for under such circumstances we would expect either a cyst or empyema of the listal portion of the organ, or perhaps even necrosis, but certainly not an obliteration unless the adhesions involved the appendix throughout its entire length and on all sides, which was not the case.

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EXFOLIATIVE CYSTITIS. A CASE REPORT.

BY J. FLETCHER ROBINSON, M. D.,
Instructor in Pathology and Bacteriology, Albany Medical College.

(From the Bender Laboratory, Albany, N. Y.)

The literature of affections of the bladder offers so few examples of cystitis with exfoliation of large portions of the bladder mucosa, that it appears justifiable to report a condition of this kind recently observed by the writer. The expulsion of a part or the whole of the mucous membrane of the bladder occurs more frequently in women, though it may be seen, rarely, in men. It is usually associated with a cystitis occurring during pregnancy, or as the result of catheterization and irrigation. Boldt,[1] after a study of a few cases of his own and of several collected from the literature, concludes somewhat as follows:

> Exfoliative cystitis is often associated with a retroverted pregnant uterus and usually manifests itself at the third or fourth month. About 50 per cent. of the cases are due to this cause. Other causes are, a retroverted myomatous uterus, the pressure made by a myoma choking the pelvis, retention of urine or the instillation of very strong, irritating solutions. The common factor underlying all the various causes is probably the ischemia produced by pressure, for cutting off or lessening of the vesical blood supply results in ischemic necrosis with or without infection. The caustic action of the ammoniacal urine in long-continued distention of the bladder may also play a part.
>
> Exfoliative cystitis usually begins with abrupt onset. The detached membrane may be extruded entire or in small pieces; the mucous surface may be so altered by the necrotic changes that it is recognizable with difficulty, and its surface is often studded with uric acid crystals. Adhering to it are often more or less extensive portions of the muscular coat, and in the worst cases the peritoneal coat is also involved.
>
> The prognosis is usually favorable except in those cases associated with sepsis. The treatment is usually that adopted for cystitis after correcting any displacements that may be present, and restoring the blood supply as nearly as possible to normal.

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[1] Boldt, *Am. Jour. of Obst.*, 1888, xxi, 361.

Dawson[1] reports a case of exfoliation of the bladder mucosa in a colored woman, the entire mucous membrane being passed *en masse* from the urethra

Norris[2] mentions a similar condition in a patient aged thirty-two, due to a virulent infection by the colon bacillus. As the acute symptoms subsided, two ounces of a five per cent. solution of silver iodide were introduced into the bladder once a day at the conclusion of irrigation. The patient improved slowly. After two weeks of treatment she was permitted to go home and was ordered to return on alternate days for treatment, but neglected to do so. One week after her discharge she returned with her urethra blocked by a sloughing mass as thick as a lead pencil, four inches of which were outside the external urinary meatus. The bladder was distended and the patient had been unable to pass urine for fourteen hours. With some difficulty an entire cast of the bladder was removed, followed by a gush of urine. Microscopic examination revealed portions of adherent muscularis. The entire specimen was undergoing necrosis.

H. C. Cochan[3] observed in a woman four months pregnant a distention of the bladder to within an inch of the ensiform cartilage, accompanied by detachment and expulsion of the entire bladder mucosa. The cast was so perfect that openings corresponding to the ureteral orifices could be readily seen. The patient was able to leave the hospital in twenty days and recovered completely.

Schabert[4] reports a case following the birth of twins.

In a case mentioned by Kelly,[5] an over distention of the bladder followed ovariotomy and portions of the mucosa were cast off.

To these reports which, though they by no means cover the entire literature represent the more important types of exfoliation, I desire to add the following:

A folded and flattened membranous mass, preserved in alcohol and resembling in a general way in color and consistence a piece of folded gutta percha membrane, was sent by Dr. I. L. Goff of Howard, N. Y., on June 16, 1906, to the Bender Laboratory with a request to determine its nature.

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[1] Dawson, *Johns Hopkins Hospital Bulletin*, 1898, ix, 155.

[2] Norris, *American Medicine*, 1906, xi, 478.

[3] Cochan, *Medical News*, 1888, lxiii, 633.

[4] Schabert, *St. Petersb. med. Woch.*, 1902, xix, 373.

[5] Kelly, Operative Gynecology, New York, 1906.

The accompanying letter stated that the patient from whom it was obtained was being treated for cystitis and had passed this substance from the urethra. The specimen, after being softened by immersion for some time in salt solution and spread out, may be described as a thin brownish yellow, irregular disk, uniform in thickness, translucent and slightly elastic and about six cm. in diameter. Microscopic examination of small portions imbedded in celloidin and stained with haematoxylin and eosin showed several imbricated layers of squamous epithelial cells arranged as are those of the normal bladder mucosa. These cells are in part necrotic and show no leucocytic infiltration. No subepithelial structures are present.

From notes furnished by Dr. Goff the following brief history was obtained. The patient, a married woman of about 40 years of age, a schoolteacher by occupation, had had two previous attacks of cystitis. During the attack characterized by the exfoliation here described she was under treatment for about one week, receiving internally, salol, acetate of potash and fluid extract of corn silk with sufficient codeine to relieve the pain. Hot normal salt solution irrigations was used at first, and later a solution of boric and tannic acids and morphine as hot as could be borne. The bowels were kept open with salines. Recovery was rapid, and no recurrence was reported. There had been two previous attacks, which were mild and unaccompanied by any exfoliation of mucous membrane.

In view of the scanty history it is impossible to arrive at any definite conclusion concerning the cause of the exfoliation. The absence of leucocytic infiltration in the material examined and also of any record of an examination of the urine forbid a statement concerning the presence of an inflammatory condition. The absence of pregnancy rules out one of the usual causes. The solutions used for irrigation are not such as usually cause injury, though Boldt quotes a case of Begonin's in which exfoliation was due apparently to the use of normal salt solution. It is possible that very hot solutions might cause necrosis and exfoliation of the mucosa, but in this instance there is no evidence that the irrigation caused the patient discomfort, as would necessarily be the case under such circumstances.

MALARIA WITH GENERAL DISTRIBUTION OF THE PLASMODIA.

By ARTHUR T. LAIRD, M. D.,
Lecturer in Clinical Microscopy, Albany Medical College.
(*From the Bender Laboratory, Albany, N. Y.*)

Records of the microscopic study of the lesions of malarial infection are, as stated by Ewing,[1] not very numerous, and much yet remains to be learned of the parasitology of the disease from microscopic studies of the visceral lesions. It has therefore seemed worth while to report the following case in which large numbers of the parasites were found in many of the organs and tissues.

*Bender Laboratory Records, Autopsy No. 535.**

Anatomical Diagnosis.—Pernicious malaria with general pigmentation most marked in the liver and spleen. Marked enlargement of the spleen. Hematogenous jaundice. Submucous hemorrhages of the stomach. Pigmentation of the mucous membranes of the stomach and intestines and of the pancreas. Cloudy swelling of the kidney, liver and heart. Chronic pleuritis (left). Hypostatic congestion and slight oedema of lungs. Atheroma effecting the bases of the mitral and aortic valves and the aorta and coronary arteries. Grayish pigmentation of the cortex of the brain. Presence of malarial parasites in the capillaries throughout the body.

The *skin, serous* and *mucous membranes*, including the conjunctiva are all very yellow, as are also the fatty tissues generally.

Liver.—27 x 16 x 10 cm. The capsule is smooth and of dark color. On section it is slate gray in color with indistinct markings. No necroses are seen. The gall-bladder measures 3.5 x 1.5 cm. and contains dark viscid bile. The bile ducts are patent.

Spleen.—6.5 x 5 x 2 cm. The capsule is smooth and free from adhesions. On section the organ is firm in consistence, deep purple in color, with prominent Malpighian corpuscles.

Kidneys.—Both are about the same size, approximately 11 x 6 x 4 cm. The capsule strips with some difficulty, bringing with it portions of the kidney substance, yet the surface for the most part is smooth. On section the organ is firm and lighter in color than normal. The cortex is narrow.

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*No clinical history could be obtained. The subject, a traveller, passing through Albany, was found dead by the hotel attendants. At the request of the coroner the autopsy was made by the writer. Only the anatomical diagnosis and those changes apparently due to malaria are given in the description of the autopsy.

Pancreas.—Measures 18 x 3 x 1 cm. On section it is bluish gray in color, otherwise appears normal.

Stomach.—In the mucous membrane of the stomach are numerous pin-point hemorrhages covering an area of 10 cm. in diameter.

Intestines.—The mucous membrane of the small and large intestines is slate gray in color.

Brain.—There is grayish pigmentation of the cortex of the brain.

Microscopic Examination.—Fresh smears made at the time of the autopsy from the *brain, bone marrow* and *spleen* show numerous intracellular parasites. These usually have the form of small spheroids, staining blue and enclosing coarse masses of brownish black pigment. In the larger forms the pigment is more scattered and finer grains are seen. No ring bodies, rosettes or crescents are found.* Sometimes a red cell contains more than one parasite. Phagocytic cells containing pigment are also seen.

Sections of various organs after Zenker and alcohol hardening were studied.

Spleen.—The pigment deposit is very extensive. Much of it is in dense masses within large phagocytic cells. There is cellular hyperplasia of the pulp tissue and the sinuses are choked and obliterated by pigmented cells. The nonpigmented cells of the Malpighian bodies stand out prominently. A very large proportion of the red cells of the pulp contain pigment or parasites. Pigment is also found within the leucocytes. The large phagocytic cells referred to are mono-nuclear, where a nucleus can be made out.

Liver.—The parasites are very numerous. They are englobed in free red cells in the capillaries or, more often, enclosed in large phagocytes together with degenerated parasites, red cells more or less degenerated, and pigment in the form of large brownish black masses and fine brownish grains. The large phagocytic cells are mono-nuclear, some of them are combined in the large protoplasmic masses described by Ewing. These fill and distend certain of the capillaries. The parasites are very much more numerous in the capillaries, nearly every red cell in which is infected, than in the larger vessels where only comparatively few of the red cells contain pigment. The liver cells show albuminous degeneration. In many of them are seen numerous fine yellow granules very different in appearance from the malarial pigment. No typical malarial pigment is found in any of the liver cells.

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*Parasites seen in fatal cases of acute malarial infection are only very rarely of the tertian type. Italian observers have claimed that tertian malaria is never fatal. Ewing has however reported a case. The aestivo-autumnal parasite is the one usually found and the one probably present in this case through this could not be demonstrated.

Bone-marrow.—The cellular hyperplasia is marked, comparatively little adipose tissue being seen. The pigment deposit is extensive but not as marked as in the liver and spleen. The pigment is found especially in large mono-nuclear cells, in the form of dense circular and irregular masses and in fine granules. A larger proportion of the red cells are uninfected than in the spleen. Pigmented spheroidal bodies are seen which are probably free parasites. Here as elsewhere no ring forms, rosettes or crescents are found. No infected nucleated red cells are seen. Eosinophilic myelocytes are numerous. The changes in the bone marrow are, in general, of the first of the two types of marrow changes described by Ewing.

Lymph Nodes.—The lymph nodes contain a moderate number of pigmented red cells. Various phagocytic cells containing pigment are also noted. Cellular hyperplasia is present and the sinuses are obliterated.

Lungs.—The capillaries here as in other organs contain immense numbers of the parasites. In many of them practically every cell is infected. The infected cells are massed in the capillaries, the larger blood vessels being comparatively free from them. Large phagocytic cells are seen distending certain of the capillaries. These cells contain masses of pigment and red cells more or less degenerated.

Cardiac Muscle.—The muscle cells show only cloudy swelling. Very large numbers of parasites are found in the capillaries. Phagocytic cells are few.

Kidney.—The intertubular capillaries contain moderate numbers of parasites. Phagocytic cells containing pigment are only rarely seen. The kidney cells show moderate degenerative changes of the albuminous type. Pigmented phagocytes and infected red cells are found in the Malpighian tufts.

Intestines.—Numerous parasites are seen in the capillaries in the mucosa and in those of the muscular fatty and connective tissues. In certain areas the epithelial cells are necrotic and there is an infiltration of round cells in the deeper layers of the mucosa. Occasional phagocytes containing pigment are seen in the capillaries.

Pancreas.—Here, also, are numerous parasites and many phagocytes containing large and small pigment granules. These are exclusively in the capillaries, no pigment being found in the parenchyma.

Brain.—Enormous numbers of parasites are found in the capillaries, nearly every red cell being infected. They are less numerous in the larger vessels. A few phagocytes containing pigment are seen.

The pathology of malaria is summed up by Mannaberg as follows: "The anatomic characteristic of acute malaria is melanemia. Microscopically this is evident in the greyish brown to graphite color of certain organs, as the spleen, liver, brain and kidneys. The pigment is found in parasites or in tissue cells (leucocytes, macrophages of the spleen, endothelial cells, marrow cells, more rarely in the parenchymatous cells of glandular organs as the liver). The distribution of the pigment in the internal organs is not uniform. It is found in the capillaries rather than in the large vessels. Dead substances like powdered glass or cinnabar if injected into the circulation distribute themselves uniformly, while bacteria show a predilection for certain situations and for certain organs. This seems to be true of the malarial parasite. The distribution varies in different cases." This is well illustrated in the study by Ewing of material collected at Camp Wikoff, Montauk Point, L. I. He reports nine cases with clinical histories and autopsies. He found that the distribution of the parasites in the internal organs was not uniform. In one case, for instance, no parasites were found in the brain, while a very abundant deposit of pigment was seen in the kidney; in another a very large number of parasites occurred in the viscera, generally, especially in the heart muscle. Still another showed a concentration of parasites in the central nervous system; in this case severe degenerative changes were present in the kidneys, though parasites were absent from the renal vessels. One case showed localization of parasites in the bone marrow.

It is generally believed that in typical cases the spleen is the first seat of malarial infection. This is borne out by the results of Craig's autopsies on the bodies of individuals dead of latent malarial infection. In these the parasites were practically localized in the spleen and had not even been demonstrated in the blood during life, though careful search had been made. The liver showed melaniferous leucocytes, but no infected red cells. Saigol reports an autopsy in a case of malaria with congenital absence of the spleen. In this case the infection attacked the mesenteric lymph nodes, which showed marked hypertrophy. Hypertrophy of the suprarenal glands was also present.

Leonard Rogers has called special attention to the frequency of pigmentation, visible to the naked eye, of the mucous membrane of the small intestine. He found it to be present in fourteen out of twenty cases examined. He believes that the continued presence of the pigment in the mucous membrane eventually causes degenerative changes and appears to be a very important factor in producing the high mortality in malarial cachexia. In the early stages the villi show in addition to deposits of black pigment, a considerable degree of thickening and distortion produced by a cellular infiltration. Changes are also found in the deeper layers of the mucous membrane; in some cases the tube glands have nearly disappeared, while their place is taken by a dense cellular infiltration. On the other hand, the muscular layers show little change. The degree of loss of absorptive and secretory power of such a membrane must be considerable. In advanced stages the process goes on to the formation of fibrous tissue and the mucous membrane becomes much atrophied.

In the case here reported the parasites have a wide distribution, being found in practically every organ. The pigmentation is very marked in the spleen and liver and brain. The changes in the intestine are similar to those described by Rogers.

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Saigol, R. D.	A Case of Transposition of the Viscera Recognized during Life. Death from Malarial Fever. Post-Mortem. Total Congenital Absence of the Spleen. *Indian Medical Gazette*, 1903, XXVIII, 417.
Rogers, Leonard.	Pigmented Atrophy of the Mucous Membrane of the Small Intestine of Malarial Origin, *Journal of Pathology and Bacteriology*, 1903, IX, 112.

BENDER HYGIENIC LABORATORY.

Annual Report of the Director for the Year Ending August 31, 1906.

To the Trustees of the Bender Hygienic Laboratory:

I have the honor to submit my report for the year ending August 31, 1906.

The Work of the Laboratory.—The routine examinations of all kinds are summarized in Table No. I.

TABLE No. I.—Routine Examinations made by the Staff of the Bender Laboratory from September 1, 1905, to August 31, 1906.

	State Department of Health.	City Department of Health.	Albany Hospital.	St. Peter's Hospital.	Child's Hospital and St. Margaret's House.	All other sources.	Total.
Autopsies			40	4	26	50	120
Surgical Specimens			1,040	280	10	141	1,471
Throat cultures	819	877				18	1,714
Sputum	423	34	1	2		72	532
Widal	150		72	36		39	297
Water, milk and ice	300					30	330
Miscellaneous	5	20				63	88
Totals	1,697	911	1,173	322	36	413	4,552

This shows an increase over each of the preceding two years, of the work done for the Albany and St. Peter's Hospitals and for the City Department of Health, but a decrease in that done for the State Department of Health. There is also an increase in the number of examinations made for private individuals and the smaller hospitals. The total number of examinations is more than one-third greater than that for either of the two previous years. This increase has been mainly along lines of surgical pathology and clinical bacteriology.

As this report marks the completion of the first decennial period of the existence of the laboratory, I have been interested in working out the amount of work done during this time. The results as given in the following table show a very satisfactory and definitely progressive increase in all lines of work. The figures are based on the examinations for each year ending August 31, and includes only those examinations of which we have records on file.

TABLE No. II.—TABLE SHOWING THE PROGRESSIVE INCREASE OF THE WORK OF THE LABORATORY DURING THE FIRST TEN YEARS OF ITS EXISTENCE.

	1897.	1898.	1899.	1900.	1901.	1902.	1903.	1904.	1905.	1906.	Totals.
Autopsies	63	66	93	92	117	123	114	123	129	120	1,040
Surgical Specimens	160	163	148	399	527	641	590	1,003	1,271	1,471	6,373
Bacteriology and Clinical Microscopy	441	367	335	789	1,595	1,977	2,120	2,515	2,683	2,961	15,783
Totals	664	596	576	1,280	2,339	2,741	2,824	3,648	4,083	4,552	23,195
Laboratory Courses	3	3	3	3	3	4	5	6	6	6	.....
Publications	2	7	8	9	10	3	8	11	8	17	83

Laboratory courses for undergraduates of the Albany Medical College have been given as follows:

1. Normal Histology.—Drs. Baldauf and Beilby, six hours a week.

2. Pathology and Bacteriology.—Drs. Pearce, Winne, Baldauf, Blackfan and Robertson, eight and a half hours a week.

3. Clinical Microscopy.—Drs. Laird and Frederick, five hours a week (class in two sections).

4. Surgical Pathology.—Drs. Elting, Carey and Sibley, two and a half hours a week.

5. Histology and Pathology, in connection with the course in Obstetrics.—Dr. Lipes, five hours a week (class in two sections).

6. Anatomy and Pathology of the Nervous System.—Dr. Archambault, one and a half hours a week.

The only change during the past year in the conduct of these courses has been the division of the class in clinical microscopy in two sections, each section working on different days in order to allow more detailed instruction. The time devoted to the work in anatomy and pathology of the nervous system has been lengthened for the year 1906-07 to two hours. As the pathology of the nervous system will in the future be more fully covered in this course, the time given general pathology has been shortened to seven and one half hours a week, while the time devoted to normal histology has been limited to five hours. Both these changes were necessary also in order to give place in the schedules of the first and second years to the two courses in experimental physiology to be inaugurated this year under the direction of Dr. H. C. Jackson, and for which facilities are available only in this laboratory.

Among those who have availed themselves of the opportunity to work in the laboratory for considerable periods of time are, Dr. D. C. Moriarta of Saratoga, Dr. Warren B. Stone and Mr. Rufus T. King of Schenectady, Drs. C. B. Hawn and J. D. Olin of Albany, Dr. J. S. Purdy of Auburn, Miss H. C. Acheson of Troy, Messrs. E. E. Tredway, J. F. Robinson, J. H. Linden, E. W. Fuller, R. P. Harris, N. K. Fromm, E. W. Jackson, G. S. Silliman and S. P. Brush of the Albany Medical College, and Mr. J. H. Musser, Jr., of the University of Pennsylvania. These have assisted in the routine work of the laboratory, pursued special lines of study or engaged in research work.

Investigations completed during the year are as follows:

1. McDonald, Ellice, Puerperal Infection; Report of Six Cases Illustrating its Varied Character. *American Medicine*, 1906, XI, 231.
2. Pearce, R. M., A Further Study of the Experimental Production of Liver Necrosis by the Intravenous Injection of Hæmagglutinative Sera. *Jour. Med. Research*, 1906, XIV, 541.
3. Pearce, R. M., Experimental Myocarditis; A Study of the Histological Changes Following Intravenous Injections of Adrenalin. *Jour. Exper. Med.*, 1906, VIII, 400.
4. Beilby, G. E., Affections of the Thyroid Gland; a Clinical and Pathological Study. *Annals of Surgery*, 1906, XLIII, 805.

5. Pease, H. D., and Pearce, R. M., Liver Necrosis and Venous Thrombosis in Horses Actively Immunized with Diphtheria and Tetanus Toxins and Streptococci and their Products. *Jour. Infec. Diseases,* 1906, III, 619.

6. Pearce, R. M., Regenerative Changes in the Liver; A Study of Experimental Lesions in the Dog. *Jour. Med. Research,* 1906, XV, 99.

7. Macdonald, W. G., Practical Bacteriological Studies in the Surgical Clinic. *Surgery, Obstetrics and Gynecology,* 1906, III, 216.

8. Archambault, J. L., and Pearce, R. M., Tuberculosis of an Adenomyoma of the Uterus. *Jour. Am. Med. Assoc.,* 1906, XLVII, 768.

9. Pearce, R. M., and Baldauf, L. K., A Note on the Production of Experimental Vascular Lesions in the Rabbit by Single Injections of Adrenalin. *Am. Jour. Med. Sciences* (in press).

10. Baldauf, L. K., The Chemistry of Atheroma and Calcification (Aorta). *Jour. Med. Research* (in press).

11. Pearce, R. M., and Jackson, H. C., Concerning the Production of Cytotoxic Sera by the Injection of Nucleoproteids. *Jour. Infect. Diseases* (in press).

12. Jackson, H. C., and Blackfan, K. D., Action of Certain Drugs on the Elimination of Uric Acid During a Nitrogen-Free Diet. *Jour. Am. Med. Assoc.* (in press).

13. Schaible, F. G., Spontaneous Amputation of an Appendix Vermiformis contained in a Femoral Hernia Sac. *Albany Medical Annals* (in press).

14. Carey, H. W., A Note on Embryonic Glandular Tumors of the Kidney with Report of a Case. *Albany Medical Annals* (in press).

15. Fromm, N. K., A Report of Four Instances in which Giant Cells Occurred in Unusual Situations with a Review of the more Important Literature of Giant Cell Formation. *Albany Medical Annals* (in press).

16. Laird, A. T., Malaria with General Distribution of the Plasmodia. *Albany Medical Annals* (in press).

17. Robinson, J. F., Exfoliative Cystitis; A Case Report. *Albany Medical Annals* (in press).

Of these investigations, the second, third, sixth, ninth, tenth and eleventh were conducted under a grant from the Rockefeller Institute for Medical Research, and the twelfth under a grant from the committee on scientific research of the American Medical Association. Study number five was carried out in collaboration with the Antitoxin Laboratory of the New York State Department of Health.

Changes in the Staff.—Dr. L. K. Baldauf, first assistant for the past year, has been reappointed for the year 1906-7. Dr. K. D. Blackfan, after one year's service as assistant, has resigned, to take up general practice in Cambridge, N. Y., and in his stead Frank George Schaible (Albany Medical College, M. D., 1905) has been appointed. Dr. La Salle Archambault is continued as assistant in Neuropathology. Dr. H. E. Robertson, assistant in surgical pathology, resigned May 1 in order to accept a position as assistant resident pathologist at the Boston City Hospital, Boston, Mass., and to this position has been appointed John Fletcher Robinson (Univ. of Michigan, B. A., 1903, Albany Medical College, M. D., 1906).

The new position of pathological house officer to the Albany Hospital, created last year, was occupied first by Dr. William M. Dwyer, and later by Dr. F. G. Schaible. For the year ending May 30, 1907, C. W. Louis Hacker (Albany Medical College, M. D., 1905) has been appointed by the board of governors of the hospital.

Mr. Leonard M. Wachter, for several years assistant chemist and bacteriologist in charge of the Albany filtration plant, resigned on September 1st, to accept a position in the laboratory of the New York State Department of Health, and to this position, with the approval of the water bureau, has been appointed Mr. George Edward Willcomb (Massachusetts Institute of Technology, S. B., 1904).

Improvements.—The only important changes have been the alteration and equipment of a room for research work in physiological chemistry for the use of Dr. H. C. Jackson, and the installation of a one-half horse power electric motor and pump, in order to supply vacuum and air pressure for general laboratory purposes.

Gifts.—Through the generosity of Dr. W. G. Macdonald, one hundred dollars was placed at our disposal for the purpose of purchasing a polariscope. The great value of this gift is shown in the fact that the apparatus has already made possible the completion of an investigation otherwise impossible, and will in the future serve a useful purpose in both the teaching and the routine work of the laboratory.

The past year has been from every point of view the most successful in the history of the laboratory. The importance of our relation to the hospitals and physicians of this neighborhood, as well as to the community generally, is indicated by the large number and variety of our routine examinations. The teaching courses, now numbering six and next year to be increased to eight, have been most satisfactory, and the value of the facilities thus afforded the Albany Medical College are apparent. The quantity and quality of our research work, as indicated by the foregoing list of publications, will, I trust, appeal to you as of great value to the future, not only of the Bender Laboratory, but also to the medical school with which this laboratory is affiliated. With this evidence before you of the satisfactory fulfillment of all the functions of a laboratory, I earnestly recommend that every effort be made to obtain for the institution an adequate financial support, in order that its efficiency may not be curtailed or its development hindered.

RICHARD M. PEARCE,
Director.

September 1, 1906.